Remarks

Reconsideration of this application is respectfully requested.

Upon entry of the foregoing amendments, claims 4-17 are pending in the application, with claim 5 being the independent claim. Claims 6, 7 and 10-13 are withdrawn. Claim 1 is presently sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 2 and 3 were previously cancelled. Claim 5 is sought to be amended to independent form. The dependency of claims 4, 14, and 16 is sought to be amended in view of the cancellation of claim 1. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Examiner Interview

Applicants thank the Examiner for the personal interview conducted with Applicants' representatives on March 18, 2010. During the interview, Applicants' representatives discussed with the Examiner the outstanding rejections of the claims. Applicants submit herewith claim amendments and comments consistent with the discussion during the interview.

II. Rejection Under 35 U.S.C. § 112, First Paragraph - Enablement

The Examiner rejected claims 1, 4, 5, 8, 9 and 14-17 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. *See* Office Action at page 2. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have cancelled claim 1 and amended claim 5 to

independent form. Applicants traverse the rejection in the event it applies to the present claims.

A. Legal Principles

In order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, the claimed invention must be enabled so that a person of skill in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Some experimentation, even a considerable amount, is not "undue" if, for example, it is merely routine. *Id.* In addition, an Applicant is not limited to the confines of the specification to provide the necessary information to enable an invention. *See In re Howarth*, 654 F.2d 103, 105-6 (CCPA 1981). Further, an Applicant need not supply information that is well known in the art. *See, e.g., Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997); *Howarth*, 654 F.2d at 105-6; *In re Brebner*, 455 F.2d 1402 (CCPA 1972).

B. In view of the teachings in the specification and the knowledge available in the art at the time the application was filed, one of ordinary skill in the art could make and use the invention without undue experimentation.

Independent claim 5 is directed to a method for treating elevated serum triglycerides comprising administering an amount of a pharmaceutical composition comprising a 5-lipoxygenase inhibitor sufficient to reduce the elevated serum triglycerides, wherein the 5-lipoxygenase inhibitor is selected from the group consisting of an acetohydroxamic acid derivative, a phenyl pyrazoline derivative, a 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone derivative, and a 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropylindol-2-yl]-2,2-dimethyl propanoic acid derivative.

For at least the following reasons, Applicants assert that in view of the teachings in the specification and the knowledge available in the art at the time the application was filed, one of ordinary skill in the art could make and use the claimed invention without undue experimentation. Thus, the enablement requirement of 35 U.S.C. § 112, first paragraph, is fully satisfied for the present claims.

(i) The specification provides the claimed classes of derivatives that inhibit 5-lipoxygenase for lowering serum triglycerides.

As an initial matter, the specification provides methods for treating elevated serum triglycerides comprising administering, for example, certain classes of derivatives that inhibit 5-lipoxygenase. *See, e.g.*, page 4, paragraph [0016]. At the time the present specification was filed, there were numerous anti-inflammatory targets in the art; however, the art did not teach the use of 5-lipoxygenase inhibitors as a class of anti-inflammatory agents that would be useful in the treatment of elevated serum triglycerides. *See, e.g.*, pages 3-4, paragraph [0014]. Moreover, agents in the art useful in the treatment of elevated serum triglycerides, such as masoprocol and curcumin, are poorly bioavailable agents and thus, must be administered in prohibitive and possibly toxic concentrations. *See, e.g.*, page 2, paragraph [0007] and pages 3-4, paragraph [0014]. As such, the present inventors fulfilled a need in the art for, and the specification provides, a new means to reduce elevated serum triglyceride levels using, for example, certain classes of derivatives that inhibit 5-lipoxygenase.

(a) Acetohydroxamic Acid Derivatives

The specification discloses that in one embodiment of the invention, the 5-lipoxygenase inhibitor is an acetohydroxamic acid derivative such as N-(3-phenoxycinnamyl)acetohydroxamic acid (CAS#106328-57-8). *See, e.g.*, page 8,

paragraph [0038]. Additional examples of acetohydroxamic acid derivatives that inhibit lipoxygenase, as well as methods for making such compounds, were known in the art at the time the present application was filed. For example, U.S. Patent No. 4,738,986 discloses a genus of compounds including N-(3-phenoxycinnamyl)acetohydroxamic acid that inhibit lipoxygenase and/or cyclooxygenase, as well as methods for the preparation of such compounds. *See, e.g.*, col. 1, lines 26-32 and Examples (copy attached as Exhibit A). U.S. Patent No. 4,713,395 discloses another acetohydroxamic acid derivative, 2-(5-chloro-4-nitro-2-methoxybenzamido) acetohydroxamic acid, as well as methods for preparation of this compound. *See, e.g.*, Abstract and Example 1 (copy attached as Exhibit B).

Accordingly, one of ordinary skill in the art would have known at the time the present application was filed numerous examples of acetohydroxamic acid derivatives that inhibit lipoxygenase as well as methods for making such compounds, and could therefore make and use the claimed invention without undue experimentation.

(b) Phenyl Pyrazoline Derivatives

The specification discloses that in another embodiment of the invention, the 5-lipoxygenase inhibitor is a phenyl pyrazoline derivative such as 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (CAS#66000-40-6) as described in Radmark *et al.*, *FEBS Lett. 110*: 213 (1980). *See, e.g.*, page 9, paragraphs [0040] and [0041]. Additional examples of phenyl pyrazoline derivatives that inhibit lipoxygenase, as well as methods of making such compounds, were known in the art at the time the present application was filed. For example, U.S. Patent Nos. 4,465,685 and 4,572,913 disclose additional phenyl pyrazoline derivatives as inhibitors of the lipoxygenase pathway that can be generated by methods in the art. *See, e.g.*, U.S. Patent No.

4,465,685 at col. 1, lines 14-22 and Abstract (copy enclosed as Exhibit C), and U.S. Patent No. 4,572,913 at Abstract (copy enclosed as Exhibit D).

Accordingly, one of ordinary skill in the art would have known at the time the present application was filed numerous examples of phenyl pyrazoline derivatives that inhibit lipoxygenase as well as methods for making such compounds, and could therefore make and use the invention without undue experimentation.

(c) 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone Derivatives

The specification discloses that in another embodiment of the invention, the 5-lipoxygenase inhibitor is a 2-(12-hydroxydodeca-5,10-iynyl)-3,5,6-trimethyl-1,4-benzoquinone (AA861) derivative. *See, e.g.*, page 9, paragraph [0042]. Additional examples of AA861 derivatives that inhibit lipoxygenase, as well as methods of making such compounds, were known in the art at the time the present application was filed. For example, U.S. Patent No. 4,393,075 discloses a genus of compounds including AA861 which exert effects on metabolic pathways involving lipoxygenase as well as methods for the synthesis of these compounds. *See, e.g.*, col. 3, lines 57-68 and Examples (copy enclosed as Exhibit E). According to the specification, derivatives of AA861 are also known in the art and disclosed, for example, in Yoshimoto *et al.*, *Biochem. Biophysica ACTA 713*:470-473 (1982) and Ashida *et al.*, *Prostaglandins 26*:955 (1993). *See, e.g.*, page 9, paragraph [0042].

Consequently, one of ordinary skill in the art would have known at the time the present application was filed numerous examples of AA861 derivatives that inhibit lipoxygenase as well as methods for making such compounds, and could therefore make and use the invention without undue experimentation.

(d) 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropyllindol-2-yl]-2,2-dimethyl propanoic acid Derivatives

The specification discloses that in another embodiment of the invention, the 5-lipoxygenase inhibitor is a 3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropyllindol-2-yl]-2,2-dimethyl propanoic acid (MK886) derivative. *See, e.g.*, pages 10 and 11, paragraph [0043]. According to the specification, derivatives of MK886 that inhibit the biosynthesis of 5-lipoxygenase metabolites of arachidonic acid are disclosed, for example, in Gillard *et al.*, *Can. J. Physiol. Pharmacolo., 67*:456-464 (1989); Rouzer *et al.*, *J. Biol. Chem., 265*:1436-1442 (1990); and U.S. Patent No. 5,081,138. *See, e.g.*, page 9, paragraph [0043]. Additional examples of derivatives of MK886 are provided in the specification, including L-669,572 (3-[l-(p-chlorobenzyl)-5-isopropyl-3-cyclopropylmethylthioindole-2-yl]-2,2-dimethylpropanoic acid); L-663,511 (3-[l-(p-chlorobenzyl)-5-isopropyl-3-phenysulfonylindol-2-yl)-2,2-dimethylpropanoic acid); L-665,210 (3-[l-(p-chlorobenzyl)-5-isopropyl-3-phenysulfonylindol-2-yl)-2,2-dimethylpropanoic acid); L-654,639 (3-[1-(p-chlorobenzyl)-5-methoxy-3-methylindol-2-yl]-2,2-dimethylpropanoic acid); L-668,017 (Rouzer *et al.*), and 3-(l-(4-chlorobenzyl)-3-(l-butyl-thio)-5-(quinolin-2-yl-methoxy)-indol-2-yl)-2,2-dimethyl propanoic acid) (MK-591) (Tagari *et al.*, *Agents Action, 40*:62-71 (1993)). *See, e.g.*, page 9, paragraph [0043].

As such, one of ordinary skill in the art would have known at the time the present application was filed numerous examples of MK886 derivatives that inhibit lipoxygenase as well as methods for making such compounds, and therefore could have been able to make and use the invention without undue experimentation.

(ii) Methods for testing the effectiveness of the claimed derivatives that inhibit 5-lipoxygenase in lowering elevated serum triglycerides, including an experimental example, are disclosed in the specification.

Additionally, the specification provides detailed methods for testing, and experimental results showing, the *in vivo* efficacy of 5-lipoxygenase inhibitors in an animal model of hypertriglyceridemia. *See, e.g.*, Examples 1 and 2. In particular, the specification provides a diet-induced animal model of hypertriglyceridemia using rats fed with a high-fructose diet and treated with 5-lipoxygenase inhibitors. Serum triglyceride levels are then analyzed in the treated rats, for example, using diagnostic kits. Figure 1 shows treatment with the phenyl pyrazoline derivative 5-lipoxygenase inhibitor, BW 755c, resulted in a significant decrease in serum triglycerides in rats fed a high fructose diet. *See, e.g.,* Figure 1, "BW-755c 100 mg/kg bid," Figure 2B, top panel "BW-755c-5," Tables 1 and 2, and Example 1 of the specification.

According to M.P.E.P. § 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." However, the specification provides working examples using the phenyl pyrazoline derivative 5-lipoxygenase inhibitor, BW 755c. According to M.P.E.P. § 2164.02, where evidence is present for one member of a claimed genus, proof of enablement is required for the other members of the genus only where adequate reasons are advanced by the Examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

Applicants have traversed the reasons advanced by the Examiner in the Office Action and have established that a person of ordinary skill in the art at the time of filing would have possessed the knowledge and skills necessary to make and use the subject

matter of the present claims without undue experimentation. As such, in view of USPTO guidance, the working examples using the phenyl pyrazoline derivative BW 755c are sufficient support for the genus of compounds of the claims.

(iii) The specification provides a correlation between the inhibition of the 5-lipoxygenase pathway and the treatment of elevated serum triglycerides.

The Examiner, in explaining the enablement rejection, alleged that no correlation has been established between 5-lipoxygenase activity and lowering serum triglycerides. *See* Office Action at page 3. Applicants respectfully disagree.

As detailed above, the specification provides:

(i) the use of certain groups of derivatives that inhibit 5-lipoxygenase in the treatment of elevated serum triglycerides;

(ii) numerous examples of such derivatives that inhibit 5-lipoxygenase and methods to make and test such compounds; and

(iii) experimental methods for testing and experimental results showing *in vivo* efficacy of 5-lipoxygenase inhibitors in animal models of hypertriglyceridemia.

In view of this description, a person of ordinary skill in the art could practice the subject matter of the present claims without undue experimentation. Undue experimentation does not mean "no" experimentation, only that it be reasonable. *See, e.g., In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). For at least the above reasons, a person of ordinary skill in the art at the time of filing would have possessed the knowledge and skills necessary to make and use the subject matter of the present claims. Thus, any experimentation required to practice the claimed methods is reasonable, not undue. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of claims 4, 5, 8, 9 and 14-17.

C. Claim 8

The above notwithstanding, Applicants note that claim 8 depends from claim 5 and specifies that the 5-lipoxygenase inhibitor is a phenyl pyrazoline derivative. Applicants further note that the BW 755c compound in the working examples is a phenyl pyrazoline derivative. *See, e.g.*, page 9, paragraph [0041] of the specification. For at least these reasons, Applicants assert that at least the elected species of phenyl pyrazoline derivatives specified in claim 8 is allowable. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection of at least claim 8.

D. Claim 9

The above notwithstanding, the Examiner indicated in the Office Action that the specification is "enabled for the treatment of elevated serum triglycerides using one 5-lipoxygenase inhibitor, BW755c." Office Action dated June 4, 2009 at page 3. Claim 9 depends indirectly from claim 5 and specifies that the 5-lipoxygenase inhibitor is 4,5-dihydro-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-amine (BW 755c). As such, it is Applicants' understanding that at least claim 9 falls within the scope of subject matter that the Examiner finds enabled by the specification. Thus, Applicants respectfully request that the enablement rejection of at least claim 9 be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph - Definiteness

At page 2 of the Office Action, the Examiner rejected claims 4, 5, 8, 9, 14 and 15 as allegedly being indefinite. Specifically, the Examiner indicates that the term "derivative" is indefinite because it is unclear how far one can deviate from the parent compounds. Office Action at page 2. Applicants respectfully traverse the rejection.

While the term "derivative" by itself may be indefinite, the term as used in the present claims is linked to compounds having a specified structural class, and the compounds within the specific structural class must also (1) be a 5-lipoxygenase inhibitor and (2) reduce elevated serum triglycerides. As discussed above, the specification provides, and one of ordinary skill would know, numerous illustrative examples of compounds within the claimed groups of derivatives, methods of making the claimed groups of derivatives, that the claimed groups of derivatives inhibit lipoxygenase, and methods for testing the effects of such compounds on elevated serum triglycerides.

Further, Applicants assert that that the term "derivative" was used in art at the time the present application was filed in the context of the claimed groups of compounds. For example, with regard to the acetohydroxamic acid derivatives specified in the claims, Applicants note that U.S. Patent No. 4,738,986 identifies the disclosed compounds as "hydroxamic acid aryl derivatives" and that U.S. Patent No. 4,713,395 identifies the disclosed compound as an "acetohydroxamic acid derivative." *See* Exhibit A at col. 1, line 8 and Exhibit B at Abstract, respectively. Therefore, by describing the claimed groups of compounds as "derivatives," Applicants are in fact using the terminology used *in the art* to describe such groups of compounds.

For at least these reasons, one of ordinary skill in the art would have recognized the groups of derivatives of the present claims based on the known use of such derivatives as inhibitors of the lipoxygenase pathway, the numerous illustrative examples in the art of such compounds, the known methods in the art of making such compounds, and the known use of the term "derivative" to describe such compounds. Therefore, for

at least these reasons, Applicants assert that one of ordinary skill in the art would clearly know the metes and bounds of the claimed derivatives.

Accordingly, Applicants submit that this terminology is definite and respectfully request that the rejection be reconsidered and withdrawn.

IV. First Supplemental Information Disclosure Statement

Applicants note that the Examiner has not provided an initialed copy of the Form PTO-1449 accompanying the First Supplemental Information Disclosure Statement filed June 22, 2004. Applicants respectfully request that the Examiner return a copy of the initialed Form PTO-1449 to Applicants and indicate that the documents cited on the form have been considered.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action. Upon the identification of otherwise allowable subject matter in a generic or linking claim, Applicants request that the Examiner examine any remaining unelected species, according to 37 C.F.R. § 1.141(a).

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Exhibit A

United States Patent [19]

Kneen et al.

[11] **Patent Number: 4,738,986**

[45] **Date of Patent: Apr. 19, 1988**

[54] **N-(3-PHENOXYCINNAMYL)ACETOHYDROXAMIC ACID**

[75] Inventors: **Geoffrey Kneen**, High Wycombe; **William P. Jackson**, Beckenham; **Peter J. Islip**, Beckenham; **Peter J. Wates**, Beckenham, all of England

[73] Assignee: **Burroughs Wellcome Co.**, Research Triangle Park, N.C.

[21] Appl. No.: **24,045**

[22] Filed: **Mar. 10, 1987**

Related U.S. Application Data

[62] Division of Ser. No. 838,534, Mar. 11, 1986.

[30] **Foreign Application Priority Data**

Mar. 16, 1985 [GB] United Kingdom 8506870
Mar. 16, 1985 [GB] United Kingdom 8506871
Mar. 16, 1985 [GB] United Kingdom 8506872

[51] **Int. Cl.**[4] C07C 83/10; A61K 31/085; A61K 31/185; A01N 3/02

[52] **U.S. Cl.** ..... 514/575; 71/68; 71/118; 260/500.5 H

[58] **Field of Search** ..... 260/500.5 H; 514/575

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,236,871	2/1966	Hinman et al.	260/500.5 H
3,306,726	2/1967	Berliner et al.	71/118
3,427,316	2/1969	Wakeman et al.	260/500.5 H
3,439,018	4/1969	Brookes et al.	260/500.5 H
3,591,623	7/1971	Back et al.	260/500.5 H
3,691,234	9/1972	Kieter et al.	260/545 R
3,825,585	7/1974	Chappelow et al.	260/500.5 H
4,169,720	10/1979	Schacht et al.	260/500.5 H
4,191,554	3/1980	Gregory	71/118
4,405,357	9/1983	Chang	260/500.5 H
4,604,407	8/1986	Haslanger et al.	260/500.5 H
4,605,669	8/1986	Summers	260/500.5 H
4,607,053	8/1986	Karenewsky et al.	260/500.5 H
4,608,390	8/1986	Summers	260/500.5 H
4,623,661	11/1986	Summers	260/500.5 H

FOREIGN PATENT DOCUMENTS

127726	1/1984	European Pat. Off. .	
161939	11/1985	European Pat. Off. .	
196674	10/1986	European Pat. Off. .	
1143265	2/1963	Fed. Rep. of Germany	260/500.5 H
1576218	2/1973	Fed. Rep. of Germany	71/118
1461338	11/1966	France	260/500.5 H
37-5178	6/1962	Japan	260/500.5 H
40-23671	10/1965	Japan	260/500.5 H
50-25730	3/1975	Japan	71/118
1136633	12/1968	United Kingdom	260/500.5 H

OTHER PUBLICATIONS

Buraczewski et al, "Bulletin De L'Academie Polonaide Des Sciences", Sep. 2, 1964, pp. 626–629, Translation.
Miyagishmia, Chem. Pharm. Bull., vol. 22, 2283, (1974).
James et al "Chem. Abstracts" 97, 178817n.
Stelzig et al, "Chem. Abstracts" 99, 85307x.
Bur–Hoe et al, "Chimie Therapeutique z (1), 39–48, (1967).
Rawson et al, Tetrahedron, vol. 26, 5653 (1970).

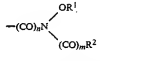
Primary Examiner—J. E. Evans
Attorney, Agent, or Firm—Donald Brown

[57] **ABSTRACT**

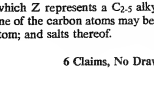
Novel compounds of formula (I)

(I)

wherein:
k, p and q are independently 0 or 1;
Ar represents either:
(i) naphthyl, tetrahydronaphthyl, pyridyl or
(ii) phenyl, optionally substituted,
L is selected from $-(CH_2)_r-$ (where r is 1–4), —O—, $-CH_2O-$, $-CH_2S-$, $-OCH_2-$, —CONH—, —NHCO—, —CO— and $-CH_2NH-$, and,
Ar' represents phenylene, thienylene or pyridylene optionally substituted,
X represents oxygen, sulphur or carbonyl,
Y is C_{1-10} alkylene or C_{1-10} alkenylene;
Q represents a non-cyclic moiety selected from groups of formula



in which one of m and n is 0 and the other is 1, R^1 and R^2 is selected from hydrogen, C_{1-4} alkyl, amino, C_{1-4} alkylamino, di-C_{1-4} alkylamino, C_{5-7} cycloalkylamino, C_{5-7} cycloalkyl (C_{1-4} alkyl) amino, anilino, N-C_{1-4} alkylanilino
or Q represents a cyclic moiety selected from 1-hydroxy-1,3-dihydroimidazol-2-one and groups of formula



in which Z represents a C_{2-5} alkylene chain in which one of the carbon atoms may be replaced by a hetero atom; and salts thereof.

6 Claims, No Drawings

N-(3-PHENOXYCINNAMYL)ACETOHYDROXAMIC ACID

This is a division of application Ser. No. 838,534 filed Mar. 11, 1986.

The present invention relates to certain compounds which are hydroxamic acid aryl derivatives, to methods of preparing such compounds, compositions containing them and to their use in medicine and in other applications.

A class of agents defined in European patent specification no. EP 0 055 418 are described therein as dual inhibitors of the lipoxygenase and cyclo-oxygenase enzymes of the mammalian arachidonic acid metabolism and were found to exhibit anti-inflammatory and related activities. Other compounds which have been described as lipoxygenase and/or cyclo-oxygenase inhibitors include certain naphthyloxy derivatives (eg as described in U.S. Pat. No. 3,740,437 or in Proc. Ann. Symp. Inst. Basic Med. Sci, Royal College of Surgeons of England, October 1982, pp 263–274). Compounds described in the latter reference include the compound known as nafazatrom..

We have now found that unexpectedly, subject to the provisos (explicit and implicit) set forth below, the compounds of formula (I) as defined hereinbelow, are particularly advantageous inhibitors of the lipoxygenase and/or cyclooxygenase enzymes and have useful medical prophylactic and therapeutic properties, as well as cerain non-medical uses.

The definition of formula (I)

$$Ar\text{—}(L\text{—}Ar')_q\text{—}(X)_k\text{—}(Y)_p\text{—}Q \qquad (I)$$

is thus:

k, p and q are independently 0 or 1, provided that when k is 1 then p must also be 1;

Ar represents either:

(i) naphthyl, tetrahydronaphthyl or pyridyl, any of which is optionally substituted by one or more substituents independently selected from C_{1-4} alkyl (which may itself optionally be substituted by one or more halogen atoms), C_{1-4} alkoxy, halo, nitro, amino, carboxy, C_{1-4} alkoxycarbonyl and hydroxy, or

(ii) phenyl optionally substituted by one or more substituents idependently selected from phenyl (optionally substituted by one or more substituents independently selected from those specified as optional substituents in (i) above) and said optional substituents specified in (i) above;

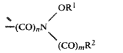
L is selected from $—(CH_2)_r—$ (where r is 1–4), —O—, $—CH_2O—$, $—CH_2S—$, $—OCH_2—$, —CONH—, —NHCO—, —CO— and $—CH_2NH—$, and,

Ar' represents phenylene, thienylene or pyridylene, any of which may be optionally substituted by one or more substituents independently selected from those specified as optional substituents in definition (i) of Ar;

X represents oxygen, sulphur or carbonyl, provided that at least one atom separates said carbonyl group from any carbonyl group in Q as defined below;

Y is C_{1-10} alkylene or C_{1-10} alkenylene;

Q represents a non-cyclic moiety selected from groups of formula



in which one of m and n is 0 and the other is 1, and when n is 1 and m is 0, R^1 and R^2 are independently selected from hydrogen and C_{1-4} alkyl, with the possibility that R^2 can also be C_{5-7} cycloalkyl, or when n is 0 and m is 1, R^1 is independently selected from hydrogen, C_{1-4} alkyl, groups as defined for Ar above and groups of formula $—COR^3$ in which R^3 is selected from C_{1-4} alkyl (optionally substituted by a carboxy or C_{1-4} alkoxycarbonyl group) and groups of formula $—N(R^4)R^5$ in which R^4 is hydrogen or C_{1-4} alkyl and R^5 represents hydrogen C_{1-4} alkyl or phenyl optionally substituted by one or more substituents independently selected from those specified as optional substituents in the definition (i) of Ar, and R^2 is selected from hydrogen, C_{1-4} alkyl, amino, C_{1-4} alkylamino, di-C_{1-4} alkylamino, C_{5-7} cycloalkylamino, C_{5-7} cycloalkyl (C_{1-4} alkyl) amino, anilino, N—C_{1-4} alkylanilino and groups as defined for Ar above;

or Q represents a cyclic moiety selected from 1-hydroxy-1,3-dihydroimidazol-2-one and groups of formula

in which Z represents a C_{2-5} alkylene chain in which one of the carbon atoms may be replaced by a hetero atom; and physiologically acceptable salts thereof and salts thereof;

with the proviso that:

when q is 0, k is 0 or 1 and p is 1, Ar is phenyl or naphthyl, either being optionally substituted by one or more substituents as specified in definition (i) of Ar, and X is oxygen or sulphur (in the case when k is 1) Y is C_{1-10} alkylene and Q represents said non-cyclic moiety as hereinbefore defined in which one of R^1 and R^2 is hydrogen or C_{1-4} alkyl;

then the other of R^1 and R^2 is neither hydrogen nor C_{1-4} alkyl.

The unexpected advantages we have found in compounds of formula (I) and their salts are selected from one or more of the following, namely: surprisingly high potency, surprising oral efficacy, surprising efficacy by inhalation and surprisingly long duration of action.

It should be appreciated that we make no claim to those compounds of formula (I) and their salts, processes for their preparation, compositions containing them and their use, which are not novel having regard to following references:

(a) Patent Specifications:

EP 0 161 939 A

GB 1 226 344 GB 1 427 114
GB 1 278 739 GB 1 437 783
GB 1 315 830 GB 1 444 492
GB 1 382 996 GB 2 047 234 A

GB 1 396 726

US 3 600 437 US 3 972 934
US 3 821 289 US 3 978 116
US 3 890 377
JP 57035543 JP 57062239

(b) Literature references:
Tetrahedron 1970 26 (23) 5653–64
Fur. J. Med. Chem. Chimica. Therapeutica 1975 10 (2) 125–128
Fur. J. Med. Chem. Chimica. Therapeutica 1970 13 (2) 211–13
J. Chem. Eng. Data 1985 30 237–9
Chem. Biol. Hydroxamic Acids [Proc. Int. Symp.] 1981, 51–62
Arzneim. Forsch. 1978 28 (11) 2087–92

Thus for example, European patent specification 0 161 939 A discloses a genus of compounds which are alleged to be anti-allergic and anti-asthmatic inhibitors of delta-5 lipoxygenase. This genus embraces compounds of formula (I) as hereinbefore defined which inter alia, are excluded by the proviso that:

when Q represents said non-cyclic moiety as hereinbefore defined,

(1) then when n is 1 and m is 0,

when q is 0 and Ar is as definition (ii) or q is 1, Ar is as definition (i) and L is —CH_2—, —O— or —CH_2O— and Ar' is phenylene optionally substituted as defined,

then at least one of k and p must be 1;

(2) and when n is 0 and m is 1,

when R^1 is hydrogen or C_{1-4} alkyl and R^2 is phenyl optionally substituted by a single substituent selected from C_{1-4} alkyl, C_{1-4} alkoxy and phenyl optionally substituted by one or more substituents independently selected from those specified as optional substituents in definition (i) of Ar,

then at least one of k and p must be 1, and in the case when k is 0 and p is 1, Y must be C_{1-10} alkenylene.

U.S. Pat. No. 3,600,437 discloses a genus of compounds said to be anti-inflammatory, analgesic and anti-pyretic agents. This genus embraces compounds of formula (I) as hereinbefore defined which are excluded by the proviso that:

when q and p are 1, k is 0, Ar is unsubstituted phenyl, L is —O—, Q is said non-cyclic moiety as hereinbefore defined, m is 0 and n is 1, L and —$(Y)_p$13 are metasubstituted relative to one another on the Ar', Ar' is phenylene and is unsubstituted or bears a substituent selected from hydroxy, amino, nitro, halo, methyl, ethyl, and C_{1-3} alkoxy and/or a substituent selected from hydroxy, halo, methyl and ethyl, R^2 is hydrogen or C_{1-4} alkyl and Y is a group of formula —CH-G—$(CH_2)_r$— in which G is hydrogen or C_{1-5} alkyl and s is 0–3;

then R^1 is C_{1-4} alkyl.

The aforementioned U.S. Pat. No. 3,600,437 also discloses inter alia, the individual compound 2-(3-phenoxyphenyl)propionohydroxamic acid.

Throughout this specification, unless indicated to the contrary, alkyl and alkyl-containing moieties (such as alkylene and alkoxy) can be either straight or branched. Alkyl of 1–4 carbon atoms whether alone or part of another moiety comprises methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and t-butyl. For use in medicine, the salts of the compounds of formula (I) are those salts which are physiologically acceptable. However, non-physiologically acceptable salts are included within the ambit of the present invention, either for use in non-medical applications such as further described hereinbelow, or as may be used in the preparation of compounds of formula (I) and their physiologically acceptable salts.

When Ar represents optionally-substituted naphthyl, this may represent naphth-1-yl or naphth-2-yl, although the latter is generally preferred.

When Ar represents optionally substituted tetrahydronaphthyl, 5, 6, 7, 8-tetrahydronaphth-1- and -2-yl are preferred, especially -2-yl.

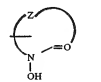
When Ar represents optionally substituted pyridyl, pyrid-2-yl and pyrid-4-yl are preferred.

When q is 1 and Ar' represents optionally substituted phenylene, —L— and —$(X)_k$— are preferably meta- or para-substituted relative to one another on the phenyl ring.

When q is 1 and Ar' represents optionally substituted thienylene, —L— and —$(X)_k$— are preferably attached in the 1- and the 5-positions of the phenylene ring.

When q is 1 and Ar' represents optionally substituted pyridylene, —L— and —$(X)_k$— are preferably attached in the 1- and the 6-positions of the pyridyline ring.

When Q represents a group of formula



and Z contains a hetero-atom, this may be sulphur, oxygen or nitrogen (—NH—). However, preferably, Z contains 3 carbon atoms. This includes the case when Z does not contain a hetero atom. Of these compounds and salts, especially preferred are those wherein Q represents -5-pyrrolidin-2-one.

One preferred sub-class of the compounds of formula (I) comprises those compounds wherein

q is 0 and p is 1;

Ar represents naphthyl optionally substituted by one or more substituents independently selected from those defined in definition (i) of Ar;

X(in the case when k is 1) is oxygen; and

Q is said non-cyclic moiety as hereinbefore defined in which n is 0, m is 1 and R^2 is C_{1-4} alkyl; and salts thereof.

An especially preferred group of compounds and salts within the latter defined sub-class comprises those wherein R^1 is hydrogen and R^2 is methyl. This group includes compounds and salts wherein Ar is unsubstituted.

q and p are 1 and k is 0.

Another preferred sub-class of the compounds of formula (I) comprises those compounds wherein

Ar represents phenyl optionally substituted by one or more substituents independently selected from those defined in definition (ii) of Ar;

L is —O— or —CH_2O—;

Ar' is phenylene optionally substituted by one or more substituents independently selected from those defined in definition (i) of Ar;

and Q is said non-cyclic moiety as hereinbefore defined, provided that when L is —CH_2O— and y is C_{1-6} alkenylene, then m is 1 and n is 0; and salts thereof.

An especially preferred group of compounds and salts within the latter defined sub-class comprises those wherein Ar and/or Ar' are substituted only by one or two fluorine atoms or both are unsubstituted, and R^2 is C_{1-4} alkyl, particularly methyl. Of this group, meta- or para-relative substitution of L and —(X)k— on Ar' is preferred.

Included within the general class of the compounds of formula (I) and their salts are the following which we may claim separately, namely those wherein:

(i) k is 1 and X represents oxygen;
(ii) k is 1 and X represents sulphur;
(iii) Q represents said non-cyclic moiety and m is 0 and n is 1;
(iv) Q represents said non-cyclic moiety and m is 1 and n is 0;
(v) Q represents a cyclic moiety as hereinbefore defined;
(vi) q is 0;
(vii) q is 1;
(viii) q is 1 and —L— is selected from —O—, —CH_2O—, —CH_2S—, —NHCO— and —CO—;
(ix) Ar' is optionally substituted phenylene;
(x) Ar' is optionally substituted thienylene;
(xi) Ar' is optionally substituted pyridylene;
(xii) Ar is optionally substituted naphthyl;
(xiii) Ar is optionally substituted tetrahydronaphthyl;
(xiv) Ar is optionally substituted pyridyl;
(xv) k is 0;
(xvi) p is 0;
(xvii) p is 1 and Y is C_{1-10} alkylene;
(xviii) p is 1 and Y is C_{1-10} alkenylene;
(xix) any two or more of (i)-(xviii) together in combination, provided the combination is compatible with the provisos contained within formula (I) as hereinbefore defined.

Preferred compounds of formula (I) include 3-phenoxy-N-methylcinnamohydroxamic acid, N-(3-phenoxycinnamyl)acetohydroxamic acid, N-(4-benzyloxybenzyl)acetohydroxamic acid, N-[2-(5,6,7,8-tetrahydro-2-naphthyloxy)ethyl]acetohydroxamic acid and N-(5,6,7,8-Tetrahydro-2-naphthylallyl)acetohydroxamic acid. Salts of the latter compounds are also preferred.

Examples of other compounds of formula (I) and their salts include the following and salts thereof.

1-Hydroxy-5-[2-(2-naphthyl)ethyl]pyrrolidin-2-one
5,6-Dihydro-N-hydroxy-5-phenyl-1,4-thiazin-3(2H,4H)-one
5-[2-(4-Biphenyl)ethyl]-1-hydroxy-2-pyrrolidone
5,6-Dihydro-4-hydroxy-6-(1-naphthyl)-1,4-thiazin-3(2H,4H)-one
6-(4-Biphenyl)-5,6-dihydro-4-hydroxy-1,4-thiazin-3(2H,4H)-one
5-(4-Biphenylyl)-1-hydroxy-2-pyrrolidone
1-Hydroxy-5-(4-isobutylphenethyl)-2-pyrrolidone
1-Hydroxy-5-phenethyl-2-pyrrolidone
1-Hydroxy-5-(3-phenylpropyl)-2-pyrrolidone
1-Hydroxy-5-[3-(6-methoxy-2-naphthyl)butyl]-2-pyrrolidone
5,6-Dihydro-4-hydroxy-6-[1-(6-methoxy-2-naphthyl)ethyl]-1,4-thiazin-3-(2H,4H)-one
5-[3-(2-Fluoro-4-biphenyl)butyl]-1-hydroxy-2-pyrrolidone
6-[1-(2-Fluoro-4-biphenyl)ethyl]-5,6-dihydro-4-hydroxy-1,4-thiazin-3(2H,4H)-one
1-Hydroxy-5-[3-(4-isobutylphenyl)butyl]-2-pyrrolidone
5,6-Dihydro-4-hydroxy-6-[1-(4-isobutylphenyl)butyl]-1,4-thiazin-3-(2H,4H)-one
N-[1-(4-biphenylyl)ethyl]acetohydroxamic acid
4-(4-biphenylyl)-N-methyl-4-oxobutanohydroxamic acid
2-(2-fluorobiphenyl-4-yl)-N-methylpropanohydroxamic acid
N-[2-(2-Fluoro-4-biphenylyl)propyl]acetohydroxamic acid
4-(2-Fluoro-4-biphenylyl)-N-methylpentanohydroxamic acid
5-(4-Biphenylyl)-N-methyl5-oxopentanohydroxamic acid
N-[2-(4-Biphenylyloxy)ethyl]acetohydroxamic acid
N-[2-(4-Biphenylyloxy)ethyl]isobutyrohydroxamic acid
N-[3-(4-Biphenylyloxy)propyl]acetohydroxamic acid
2-(4-Biphenylyloxy)-N-methylacetohydroxamic acid
3-(4-Biphenylyloxy)-N-methylpropionohydroxamic acid
7-(4-Biphenylyloxy)-N-methylheptanohydroxamic acid
3-(4-Biphenylyl)-N-methylpropionohydroxamic acid
5-(4-Biphenylyl)-N-methylpentanohydroxamic acid
N-Methyl-2-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)acetohydroxamic acid
N-Methyl-3-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)-propionohydroxamic acid
N-Methyl-7-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)-heptanohydroxamic acid
Methyl N-methyl-3-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)propionohydroxamate
N-[3-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)propyl]acetohydroxamic acid
N-[6-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)hexyl]acetohydroxamic acid
N-[2-(5,6,7,8-tetrahydro-1-(or 2-)naphthoxy)ethyl]isobutyrohydroxamic acid
N-Methyl-3-(5,6,7,8-tetrahydro-1-(or 2)naphthyl)propionohydroxamic acid
N-Methyl-5-(5,6,7,8-tetrahydro-1-(or 2-)naphthyl)pentanohydroxamic acid
N-[3-(5,6,7,8-tetrahydro-1-(or 2-)naphthyl)propyl]acetohydroxamic acid
N-[5-(5,6,7,8-tetrahydro-1-(or 2-)naphthyl)pentyl]acetohydroxamic acid
N-[3-(5,6,7,8-tetrahydro-1-(or 2-)naphthyl)propyl]isobutyrohydroxamic acid
N-[2-(2-naphthyloxy)ethyl]benzohydroxamic acid
2-Benzyloxy-N-methylbenzohydroxamic acid
N-methyl-3-benzyloxybenzohydroxmic acid
4-benzyloxy-N-methylbenzohydroxamic acid
N-methyl-3-(2-naphthyloxymethyl)benzohydroxamic acid
3-(2-biphenylyloxymethyl)-N-methylbenzohydroxamic acid
4-(4-biphenylyloxymethyl)-N-methylbenzohydroxamic acid
N-methyl-2-[5-methyl-2-(4-methylphenylcarbamoyl)-phenoxy]acetohydroxamic acid,
N-[1-(4-benzyloxy-2-hydroxyphenyl)ethyl]-acetohydroxamic acid
N-(2-benzyloxybenzyl)acetohydroxamic acid, viscous oil
2-(3-benzoylphenyl)-N-methylpropionohydroxamic acid
N-methyl-4-(3-propoxybenzoyl)benzohydroxamic acid
N-[4-(1-naphthylmethoxy)benzl]acetahydroxamic acid
N-(3-phenoxybenzyl)acetohydroxamic acid
N-(3-benzyloxybenzyl)acetohydroxamic acid

N-methyl-3-(1-naphthyloxymethyl)benzohydroxamic acid
3-benzylamino-N-methylbenzohydroxamic acid
4-benzylamino-N-methylbenzohydroxamic acid
5-benzyloxy-2-hydroxy-N-methylbenzohydroxamic acid
4-benzyloxy-2-hydroxy-N-methylbenzohydroxamic acid
4-benzamido-N-methylbenzohydroxamic acid
3-benzamido-N-methylbenzohydroxamic acid
3-benzoyl-N-methylbenzohydroxamic acid
5-benzoyloxy-N-methylthiophen-2-carbohydroxamic acid
4-benzoyloxy-N-methylthiophen-2-carbohydroxamic acid
3-(biphenyl-2-yloxymethyl)-N-methylbenzohydroxamic acid
N-methyl-3-(1-naphthyl)propenohydroxamic acid
N-methyl-4-methylcinnamohydroxamic acid
2-benzyloxy-N-methylcinnamohydroxamic acid
N-Methyl-3-trifluoromethylcinnamohydroxamic acid
N-Methyl-3-phenoxybenzohydroxamic acid
N-Methyl-4-phenoxybenzohydroxamic acid
2-(4-Biphenylyl)-N-methylpropanohydroxamic acid
N-Methyl-3-(3-propoxybenzoyl)benzohydroxamic acid
N-(Cyclohexyl)-2-[4-(2-methylpropyl)phenyl]-propanohydroxamic acid
N-Methyl-3-(2-naphthyl)propenohydroxamic acid
2-(2-Fluorobiphenyl-4-yl)-N-cyclohexylpropanohydroxamic acid
2-(2-Fluorobiphenyl-4-yl)-N-t-butylpropanohydroxamic acid
N-(1,1-Dimethylethyl)-3-phenoxycinnamohydroxamic acid
2-(4-Biphenylyloxy)-N-methylpropanohydroxamic acid
N-[1-(4-Biphenylyl)ethyl]acetohydroxamic acid
N-(4-Biphenylylmethyl)acetohydroxamic acid
N-[4-(2-Naphthylmethoxy)benzyl]acetohydroxamic acid
N-(4-Phenoxybenzyl)acetohydroxamic acid
N-(4-Benzyloxybenzyl)pivalohydroxamic acid
2-(2-Fluoro-4-biphenylyl)-N-isopropylpropanohydroxamic acid
N-(4-Benzyloxybenzyl)-2-methylpropanohydroxamic acid
N-(4-Phenylcarbamoylbenzyl)acetohydroxamic acid
N-[(2',4'-Difluoro-4-biphenylyl)methyl]acetohydroxamic acid
N-[1-(2',4'-Difluoro-4-biphenylyl)ethyl]-2,2-dimethylpropanohydroxamic acid
N-[4-(4-Biphenylylmethoxy)benzyl]acetohydroxamic acid
N-[4-(2,4-Difluorobenzyloxy)benzyl]acetohydroxamic acid
N-[4-(2,4-Difluorobenzyloxy)benzyl]pivalohydroxamic acid
N-[5,6,7,8-Tetrahydro-2-naphthyl)methyl]acetohydroxamic acid
N-[2-(5,6,7,8-Tetrohydro-2-naphthyloxy)ethyl]-pivalohydroxamic acid
N-(5,6,7,8-Tetrahydro-2-naphthylallyl)pivalohydroxamic acid
N-(5,6,7,8-Tetrahydro-2-naphthylmethyl)pivalohydroxamic acid
N-[2-(2',4'-Difluoro-4-biphenyl)ethylacetohydroxamic acid
N-(4-Isobutylbenzyl)acetohydroxamic acid
N-[1-(4-Biphenyl)ethyl]pivalohydroxamic acid
N-[(4-Biphenylyl)methyl]pivalohydroxamic acid
5-[2-(4-Benzyloxyphenyl)ethyl]-1-hydroxy-2-pyrrolidone
5,6-Dihydro-4-hydroxy-6-(2-naphthyl)-1,4-thiazin-3(2H,4H)-one
6-(4-Benzyloxyphenyl)-5,6-dihydro-4-hydroxy-1,4-thiazin-3(2H,4H)one
1-Hydroxy-1-[2-(2-naphthyloxy)ethyl]-3-phenylurea
N-(4-Benzyloxybenzyl)-N-hydroxy-N-methylurea
3-(4-Benzyloxybenzyl)-1,3-dihydro-1-hydroxyimidazol-2-one
1,3-Dihydro-1-hydroxy-3-(4-phenylbenzyl)imidazol-2-one
N-(4-Benzyloxybenzyl)-O-methylcarbamoylacetohydroxamic acid
N-[2-(2-Naphthylthio)ethyl]-N-(phenylcarbamoyloxy)acetamide
N-[4-(Benzyloxybenzyl)-O-(methylcarbamoyl)-pivalohyroxamic acid
N-(4-Benzyloxybenzyl)-O-(2,2-dimethylethyl)carbamoylacetohydroxamic acid
N-(4-Benzyloxybenzyl)-N-(t-butylcarbonyloxy)acetamide
3-[N-(4-Benzyloxybenzyl)acetamidooxycarbonyl]-propanoic acid
N-[3-(4-Benzyloxyphenyl)prop-2-enyl]acetohydroxamic acid
N-(3-Phenoxycinnamyl)acetohydroxamic acid
N-[2-(4-Biphenylyloxy)ethyl]acetohydroxamic acid
4-(Biphenyl-4-yloxy)-N-methylbut-2-enohydroxamic acid
3-(3-Fluoro-4-phenoxyphenyl)-N-methylprop-2-enohydroxamic acid
N-[3-(4-Benzyloxyphenyl)prop-2-enyl]acetohydroxamic acid
N-[4-(2-Pyridyl)benzyl]acetohydroxamic acid
N-[4-(2,4-Difluorophenoxymethyl)benzyl]acetohydroxamic acid
N-[4-(2-Pyridyloxy)benzyl]acetohydroxamic acid
N-(5-Phenoxymethyl-2-thienylmethyl)acetohydroxamic acid
3-(4-Fluoro-3-phenoxyphenyl)-N-methylprop-2-enohydroxamic acid
N-(6-Phenoxy-2-pyridylmethyl)acetohydroxamic acid
N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]acetohydroxamic acid
N-[4-(Benzylthio)benzyl]acetohydroxamic acid
N-[3-(2-Pyridyloxy)benzyl]acetohydroxamic acid
N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-methylurea
N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-t-butylurea
N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-cyclohexylurea
N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-phenylurea
N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-methylurea
N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-t-butylurea
N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-cyclohexylurea
N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-phenylurea
N-Hydroxy-N'-methyl-N-[3-(2-pyridyloxy)benzyl]urea
1-Hydroxy-3-(3-phenoxybenzyl)-1,3-dihydroimidazol-2-one
1-Hydroxy-3-(6-phenoxy-2-pyridylmethyl)-1,3-dihydroimidazol-2-one
3-(2-Pyridyloxy)prop-2-enohydroxamic acid
1-Hydroxy-5-(2-pyridyl)piperazin-2-one

N-(2-[4-(2-Pyridylmethoxy)phenoxy]ethyl)acetohydroxamic acid
N-(2-[3-(2-Pyridylmethoxy)phenoxy]ethyl)acetohydroxamic acid
N-(2-[4-(Benzyloxy)phenoxy]ethyl)acetohydroxamic acid
N-[4-Fluoro-2-phenoxyphenyl)methyl]-N-hydroxy-N'-methylurea
N-[4-Fluoro-3-phenoxyphenyl)methyl]-N-hydroxy-N'-phenylurea
N-[3-(Biphenyl-4-yl)prop-2-enyl]-N-hydroxy-N'-methylurea
N-[3-(Biphenyl-4-yl)prop-2-enyl]-N-hydroxy-N'-phenylurea
N-[(4-Benzyloxyphenyl)methyl]-N-hydroxyurea
N-[(4-Benzyloxyphenyl)methyl]-N-hydroxy-N'-methylurea
N-[4-hydroxybenzyloxy)benzyl]acetohydroxamic acid
N-[4-(4-pyridylmethoxy)methyl]acetohydroxamic acid
3-[(4-Fluoro-3-phenoxyphenyl)methyl]-1-hydroxy-1,3-dihydroimidazol-2-one
3-[(2-Fluorobiphenyl-4-yl)methyl]-1-hydroxy-1,3-dihydroimidazol-2-one
1-Hydroxy-3-[3-(4-phenoxyphenyl)prop-2-enyl]-1,3-dihydroimidazol-2-one
3-]4-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-1-hydroxy-1,3-dihydroimidazol-2-one

Further examples of compounds of formula (1) include each and every specific compound listed below:
N-Methyl-3-(Ar)acrylohydroxamic acid,
N-Methyl-5-(Ar)-2,4-pentadienohydroxamic acid,
N-Methyl-4-(4-isobutylphenyl)-2-butenohydroxamic acid,
N-[3-(Ar)-2-propenyl]acetohydroxamic acid and
N-[3-(Ar)-2-propenyl]isobutyrohydroxamic acid
wherein Ar represents
(i) 1 (or 2)-naphthyl
(ii) 4-isobutylphenyl
(iii) 4-biphenylyl
(iv) 2 (or 3 or 4)-benzyloxyphenyl
(v) phenyl or
(vi) 4-methylphenyl

It should be appreciated that any compound in the foregoing list may be claimed alone or with one or more of the others as constituting a preferred aspect of the present invention.

Subject to any limitations expressed implied herein, the present invention also provides any compound of formula (I) (as hereinbefore defined) or physiologically acceptable salt thereof for use as an inhibitor of the lipoxygenase and/or cyclo-oxygenase enzymes of the mammalian arachidonic acid metabolism, to methods of inhibition of such enzyme(s) by administration to a mammal of a lipoxygenase and/or cyclo-oxygenase (as appropriate) inhibiting amount of any such compound or salt, and to use of any such compound or salt in the manufacture of lipoxygenase and/or cyclo-oxygenase inhibitor (as appropriate) agents.

Further, and also subject to any limitations expressed or implied herein, the present invention also provides any compound of formula (I) (as hereinbefore defined) or physiologically acceptable salt thereof, for use as a medical therapeutic and/or prophylactic agent, to methods of medical therapeutic and/or prophylactic treatment by administration to a mammal of a medically therapeutic and/or prophylactic (as appropriate) effective amount of any such compound or salt, and to use of any such compound or salt in the manufacture of medical therapeutic and/or prophylactic (as appropriate) agents. The kinds of medical therapy and prophylaxis pertinent to the foregoing and therefore in that sense comprising part of the present invention, are elaborated by way of example in the following paragraphs which are not intended to be construed as in any way limiting the scope of these aspects of said invention.

By virtue of their lipoxygenase inhibitory properties, said compounds and salts find application in the treatment and/or prophylaxis of any condition where a lipoxygenase inhibitor is indicated, especially spasmogenic and allergic conditions and tumors.

By virtue of their cyclo-oxygenase inhibitory properties, said compounds and salts find application in the treatment and/or prophylaxis of any condition where a cyclo-oxygenase inhibitor is indicated, especially pyresis and pain.

By virtue of both their lipoxygenase and cyclo-oxygenase inhibitory properties, said compounds and salts find application in the treatment and/or prophylaxis of any condition where a dual lipotygenase/cyclo-oxygenase inhibitor is indicated, especially any condition involving blood platelet aggregation or inflammation. In the case of inflammation, the compounds and salts are particularly suited to the treatment and/or prophylaxis of conditions associated with infiltration of leucocytes into inflamed tissue.

In determining when a lipoxygenase, cyclo-oxygenase or dual lipoxygenase/cyclo-oxygenase inhibitor is indicated, of course inter alia, the particular condition in question and its severity must be taken into consideration and this determination is ultimately at the discretion of the attendant physician.

Examples of the aforesaid spasmogenic conditions are those involving smooth muscle tissue, especially airway smooth muscle constriction such as intrinsic asthma (including intrinsic or idiopathic bronchial asthma and cardiac asthma), bronchitis and arterial smooth muscle constriction such as coronary spasm (including that associated with myocardial infarction, which may or may not lead to left ventricular failure resulting in cardiac asthma) and cerebral spasm or 'stroke'. Other examples include bowel disease caused by abnormal colonic muscular contraction such as may be termed 'irritable bowel syndrome', 'spastic colon' or 'mucous colitis'.

Examples of the aforesaid allergic conditions are extrinsic asthma (from which it will be appreciated that said compounds and salts are particularly favourable as anti-asthmatic agents), allergic skin diseases such as eczema having a total or partial allergic origin, allergic bowel disease (including coeliac disease) and allergic eye conditions such as hayfever (which may additionally or alternatively affect the upper respiratory tract) and allergic conjunctivitis. Examples of the aforesaid tumours are skin neoplasms, both benign and malignant.

Examples of the aforesaid pyretic and painful conditions include fever associated with infections, trauma and injury, malignant disease, and diseases affecting the immune system (including anto-immune disease).

Examples of the aforesaid conditions involving blood platelet aggregation are those resulting from thrombosis, including 'stroke' having a total or partial thrombotic origin, coronary thrombosis, phlebitis and phlebothrombosis (the latter two conditions also possibly being associated with inflammation).

Examples of the aforesaid conditions involving inflammation are inflammatory conditions of the lung, joints, eye, bowel, skin and heart.

Inflammatory lung conditions which may be so treated and/or prevented include asthma and bronchitis (vide supra) and cystic fibrosis (which may also or alternatively involve the bowel or other tissue).

Inflammatory joint conditions which may be so treated and/or prevented include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

Inflammatory eye conditions which may be so treated and/or prevented include uveitis (including iritis) and conjunctivitis (vide supra).

Inflammatory bowel conditions which may be so treated and/or prevented include Crohn's disease and ulcerative colitis.

Inflammatory skin diseases which may be so treated and/or prevented include those associated with cell proliferation, such as psoriasis and eczema (vide supra) and dermatitis (whether or not of allergic origin).

Inflammatory conditions of the heart which may be so treated and/or prevented include coronary infarct damage.

Other inflammatory conditions which may be so treated and/or prevented include tissue necrosis of chronic inflammation and tissue rejection following transplant surgery. It is also believed that the compound of formula (I) and their physiologically acceptable salts are effective agents in the prophylaxis and/or treatment of bacterial and fungal infections, this forming a further aspect of the present invention in like manner.

It is known in the literature that some compounds which are cyclo-oxygenase and/or lipoxygenase inhibitors can delay the decay of cut plant matter. Thus, it is now believed that by virtue of their enzyme inhibitory effects, the compounds of formula (I) and salts thereof are also useful for controlling the processes of growth and decay in plants. Thus the present invention also provides the compounds of formula (I) and their salts for use in a method of regulating the growth of, or delaying senescence in vegetable matter by application to said matter of an effective amount of a compound of formula (I) or a salt thereof.

The term senescence refers to the process whereby plant matter decays, especially after being picked, cut or otherwise removed from its normal growing environment. Vegetable matter includes trees, shrubs, flowers and edible vegetables and other food crops.

The above method is particularly applicable to flowers intended for decorative or display purposes such as carnations, crysanthemums, daisies, begonias, etc. These include perennial annual and biannual flowers, for example those that grow from bulbs (eg dahlias) or from seed (eg marigolds). The method is also especially suited to use with decorative shrubs and trees, for example those which are displayed when cut, such as christmas trees.

The compound of formula (I) and their salts may also be used for the preservation of picked fruits.

For medical use, the amount required of a compound of formula (I) or physiologically acceptable salt thereof (hereinafter referred to as the active ingredient) to achieve a therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment and the particular disorder or disease concerned. A suitable dose of a compound of formula (I) or physiologically acceptable salt thereof for a mammal suffering from, or likely to suffer from any condition as described hereinbefore is 0.1 μg–500 mg of base per kilogram bodyweight. In the case of systemic administration, the dose may be in the range 0.5 to 500 mg of base per kilogram bodyweight, the most preferred dosage being 0.5 to 50 mg/kg of mammal bodyweight for example 5 to 25 mg/kg; administered two or three times daily. In the case of topical administration, eg. to the skin or eye, a suitable dose may be in the range 0.1 ng–100 μg of base per kilogram, typically about 0.1 μg/Kg.

In the case of oral dosing for the treatment or prophylaxis of airway smooth muscle constriction, or asthma or bronchitis in general, due to any course, a suitable dose of a compound of formula (I) or physiologically acceptable salt thereof, may be as specified in the preceding paragraph, but most preferably is from is 1 mg to 10 mg of base per kilogram, the most preferred dosage being from 1 mg to 5 mg/kg of mammal bodyweight, for example from 1 to 2 mg/kg. In the case of pulmonary administration for the latter indications, the dose may be in the range of from 2 μg to 100 mg, for example from 20 μg to 0.5 mg, especially 0.1 to 0.5 mg/kg.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising a compound of formula (I) or a pharmacologically acceptable acid addition salt thereof and a physiologically acceptable carrier therefor. Such formulations consitute a further feature of the present invention. Conveniently, the active ingredient comprises from 0.1% to 99.9% by weight of the formulation. Conveniently, unit doses of a formulation contain between 0.1 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 2% by weight of the formulation but the active ingredient may comprise as much as 10% w/w. Formulations suitable for nasal or buccal administration, (such as self-propelling powder dispensing formulations described hereinafter), may comprise 0.1 to 20% w/w, for example 2% w/w of active ingredient.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical, nasal or buccal administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active ingredi-

ent; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented in the form of aqueous eye drops as, for example, a 0.1–1.0% solution. Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations such as aerosols and atomizers. The formulations, when dispersed, preferably have a particle size in the range of 0.1 to 200μ.

A particularly valuable form of a pharmaceutical composition of the present invention, for use in the prophylaxis or treatment of airway smooth muscle constriction, or asthma or bronchitis in general, due to any cause, is one suitable for pulmonary administration via the buccal cavity. Preferably the composition is such that particles having a diameter of 0.5 to 7μ, most preferably 1 to 6μ, containing active ingredient, are delivered into the lungs of a patient. Such compositions are conveniently in the form of dry powders for administration from a powder inhalation device or self-propelling powder-dispensing containers, for example as a self-propelling aerosol composition in a sealed container; preferably the powders comprise particles containing active ingredient of which particles at least 98% by weight have a diameter greater than 0.5μ and at least 95% by number have a diameter less than 7μ. Most desirably at least 95% by weight of the particles have a diameter greater than 1μ and at least 90% by number of particles have a diameter less than 6μ.

The compositions in the form of dry powders preferably include a solid fine powder diluent such as sugar and are conveniently presented in a pierceable capsule, for example of gelatin.

Self-propelling compositions of the invention may be either powder-dispensing compositions or compositions dispensing the active ingredient in the form of droplets of a solution or suspension. Self-propelling powder-dispensing compositions include a liquid propellant having a boiling point of below 65° F. at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% w/w of the composition whilst the active ingredient may constitute 0.1 to 20% w/w, for example about 2% w/w of the composition. The carrier in such compositions may include other constituents, in particular a liquid non-ionic or solid anionic surfactant, or a solid diluent (preferably having a particle size of the same order as of the particles of active ingredient) or both. The surfactant may constitute from 0.01 up to 20% w/w, though preferably it constitutes below 1% w/w of the composition.

Self-propelling compositions wherein the active ingredient is present in solution comprise an active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. The co-solvents may constitute 5 to 40% w/w of the composition, though preferably less than 20% w/w of the composition.

Compositions of the present invention may also be in the form of aqueous or dilute alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser.

Formulations of the present invention may also be in the form of an aqueous or dilute alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. Such formulations usually contain a flavouring agent such as saccharin sodium and a volatile oil. A buffering agent and a surface active agent may also be included in such a formulation which should also contain a preservative such as methylhydroxybenzoate.

Other formulations suitable for nasal administration include a coarse powder having a particle size of 20 to 500 microns which is administered in the manner in which snuff is taken i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives eg. methylhydroxybenzoate (including anti-oxidants), emulsifying agents and the like. Any other therapeutic ingredient may comprise one or more of the following: antibiotic (e.g. anti-bacterial), anti-fungal and anti-viral agents, and anti-histamines (particularly peripherally acting anti-histamines). However, when such other agent(s) are also present, according to another aspect of the invention, the compound of formula (I) or physiologically acceptable salt thereof and the other agent(s), need not necessarily be present as a pharmaceutical formulation as hereinbefore defined, but merely in combination or intimate admixture, i.e. optionally, a pharmaceutically acceptable carrier need not be present. The combination with anti-histamines is particularly favoured for anti-asthmatic use. Such an anti-histamine may be selected from any compound described in European Patent Applications EP 0 859 959 A and EP 0 117 302 A. The amount and dosage regime for such an anti-histamine may be chosen from any of those recited in the latter two European Specifi-

cations. Especially preferred are the anti-histamines (E)-3-(6-(3-pyrrolidino-1-(4-tolyl)prop-1E-enyl(-2-pyridyl)acrylic acid and (E)-3-(6-(3-pyrrolidino-1-(4-tolyl)prop-1E-enyl(-2-pyridyl)propionic acid. Another preferred anti-histamine is (E)-1-(4-methylphenyl)-1-(2-pyridyl)-3-pyrrolidinoprop-1-ene, otherwise known as triprolidine.

For delaying senescence of cut or picked plant matter, or for controlling plant growth, the compounds of formula (I) and their salts re preferably presented in a suitable composition, optionally containing one or more other agents for enhancing the freshness of the plants. Such compositions include solutions and suspensions of the compound in a suitable medium such as an aqueous medium.

The compositions may be applied by immersing part (eg the cut end) or whole of the plant or by spraying the plants before ar after cutting or picking, or by application to the root structure before or after picking. The compounds may also be applied by being spread on the soil prior to cutting or picking and conveyed to the plant roots by rainwater, or by other watering means.

When applied in aqueous solution, the compounds may be presented in a concentration of from 1 μM to 1M, for example 100 μM to 100 mM. A typical concentration might be about 1 mM.

The compounds of formula (I) and their salts may be prepared by the following process which (subject to any provisos expressed herein) constitutes a further aspect of the present invention:

(a) for the preparation of compounds of formula (I) in which Q represents a non-cyclic moiety (as hereinbefore defined) in which R^1 represents hydrogen, reacting a compound of formula (II)

$$R^6NHOH \quad (II)$$

with a compound of formula (III)

$$R^7—R^8 \quad (III)$$

(in which one of R^6 and R^7 is a group R^2 as hereinbefore defined and the other is a group of formula Ar—(-L—Ar')$_q$—(X)$_k$—(Y)$_p$— as hereinbefore defined, and R^8 is a group capable of reacting with the NH group in the compound of formula (II) thereby to bring about formation of the corresponding hydroxamic acid or derivative thereof);

(b) for the preparation of compounds of formula (I) in which Q represents a non-cyclic moiety (as hereinbefore defined) in which R^1 represents hydrogen, n is 1 and m is 0, reacting a compound of formula (IV)

$$Ar—(L—Ar')_q—(X)_k—(Y)_p—CH=O \quad (IV)$$

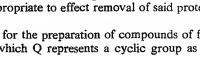
(wherein q, k, p, Ar, Ar', L, X and Y are as hereinbefore defined) with Piloty's acid, i.e. the compound of formula $PhSO_2NHOH$, or an appropriate analogue or derivative thereof;

(c) for the preparation of compounds of formula (I) in which Q represents a non-cyclic moiety (as hereinbefore defined) in which R^1 represents hydrogen, reacting a compound of formula (V)

$$R^9N(OZ^1)H \quad (V)$$

(wherein R^9 is a group R^2 as hereinbefore defined or a group of formula Ar—(L—Ar')$_q$—(X)$_k$—(Y)$_p$— as hereinbefore defined, as appropriate, and Z^1 is hydrogen or an appropriate protecting group) with an appropriate acylating agent, and where Z^1 is a protecting group, subjecting the reaction product to such conditions and/or reacting with one or more reagents as appropriate to effect removal of said protecting group; or;

(d) for the preparation of compounds of formula (I) in which Q represents a cyclic group as hereinbefore defined, treating a compounds of formula (VI)



(VI)

(where Ar, Ar', L, X, Y, q, k and p are as hereinbefore defined and R^{10}-R^{11}-R^{12} are chosen to be capable of cyclisation) with an agent or agents and under such reaction conditions to bring about cyclisation of said R^{10}-R^{11}-R^{12};

and optionally if desired, effecting one or more of the following interconversions in any desired order:

(i) when in the compound of formula (I) so formed, any of R^1, R^2 and (in the definition of R^1) R^4 and R^5 are hydrogen atoms, converting said compound to a corresponding compound of formula (I) wherein any of said hydrogen atoms as desired, are converted to C_{1-4} alkyl groups;

(ii) converting the compound of formula (I) to a corresponding salt thereof;

(iii) when in the compound of formula (I) so formed, n is 0, m is 1 and R^1 is hydrogen, converting said compound to a corresponding compound of formula (I) wherein R^1 is a group of formula —COR^3 as hereinbefore defined;

(iv) when a compound of formula (I), n is 0, m is 1 and R^1 is a group of formula —COR^3 in which R^3 is a C_{1-4} alkyl group substituted by carboxy, converting said compound to a corresponding compound in which R^3 is C_{1-4} alkyl substituted by C_{1-4} alkoxycarbonyl.

In process option (a) above, the compound of formula (II) may be used in the form of a salt thereof and the compound of formula (III) for example is an appropriate mixed anhydride or activated acid such as an acid halide (e.g. the chloride). Preferably, the reaction is effected in a suitable solvent and where the compound of formula (II) is in the form of a salt, in the presence of a base, such as an appropriate amine, to liberate the free hydroxylamine compound in situ.

Process option (b) may for example be effected in the presence of a base such as an alkali metal hydroxide or alkoxide, e.g. sodium hydroxide or sodium methoxide.

In process option (c), where the group Z^1 in the compound of formula (V) is a protecting group, this may for example be selected from an acetyl, benzyl, O-benzyl, trityl, tetrahydropyranyl, O-tetrahydropyranyl, O-t-butyl and benzoyl. The protecting group may be removed by treatment with acid or base or by hydrogenation as will readily be apparent to those skilled in the art. In general, suitable protecting groups and methods for their removal will be found in T. W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1981. Particular examples of removal of such leaving groups include removal of an O-benzyl group by hydrogenolysis over 5% palladium on charcoal at room tem-

perature, or removal of O-tetrahydropyranyl with pyridinium para-toluene sulphate in refluxing methanol.

When process option (c) is used to prepare a compound of formula (I) wherein Q represents a non-cyclic moiety (as hereinbefore defined) in which n is 0 and m is 1, R^2 is an amino group or a mono-amine derivative and Z^1 is a protecting group the acylating agent may be an isocyanate of formula (VII).

$$Q^1NCO \qquad (VII)$$

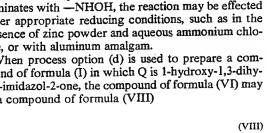
(wherein Q^1 is said R^2 group minus the —NH portion) and the reaction is effected in a suitable solvent such as toluene, optionally at a temperature above ambient.

When process option (c) is used to prepare a compound of formula (I) in which Q represents a non-cyclic moiety (as hereinbefore defined) and R^2 is other than as specified in the preceding paragraph (whether Z is hydrogen or a protecting group), the acylating agent may for example be an appropriate mixed anhydride or activated acid, such as an acid halide (for example chloride),

When process option (d) is used to prepare a compound of formula (I) in which Q is a group of formula

(wherein Z is as hereinbefore defined) one of the groups R^{10} and R^{12} may terminate with a group of formula $—CO_2Q^2$ (where Q^2 is hydrogen, amino, C_{1-6} alkyl or aryl (e.g. phenyl)) and the other then terminates with an appropriate reactive group such as a group of formula $—OQ^3$ (wherein Q^3 *is hydrogen or a protecting group such as benzyl or any of those defined above in respect of* Z^1) or else the other terminates with a group of formula $—NO_2$ or —NHOH. Generally, the reaction may be effected in a suitable solvent such as toluene, in the presence of an acid catalyst such as para-toluenesulphonic acid, if necessary at an elevated temperature. When one of R^{10} and R^{12} terminates with —NHOH, the reaction may be effected under appropriate reducing conditions, such as in the presence of zinc powder and aqueous ammonium chloride, or with aluminum amalgam.

When process option (d) is used to prepare a compound of formula (I) in which Q is 1-hydroxy-1,3-dihydro-imidazol-2-one, the compound of formula (VI) may be a compound of formula (VIII)



(VIII)

(wherein Ar, Ar', L, X, Y, q, k and p are as hereinbefore defined) and the cyclisation may be initiated by removal of the acetal group with an appropriate reagent such as trifluoroacetic acid.

Optional conversion (i) may for example be effected by reaction with an appropriate alkyl halide or sulphate in the presence of a mild base. Where one or more but not all of a number of hydrogen atoms are to be selectively alkylated, the conversation may require one or more steps of protection and subsequent deprotection.

Optional conversion (ii) conveniently may be effected by reaction with an appropriate organic or mineral acid, or with a base.

Optional conversion (iii) when used for the preparation of compounds wherein R^3 is a group of formula $—N(R^4)R^5$, may comprise reacting the compound of formula (I) with an appropriate isocyanate, suitably in an appropriate solvent such as tetrahydrofuran or toluene, optionally in the presence of a catalyst such as 1,8-diazabicyclo[5.4.0]undec-7-ene.

Optional conversion (iii) when used for the preparation of compounds wherein R^3 is an alkyl group optionally substituted by a carboxy group or a C_{1-4} alkoxycarbonyl group, may comprise reacting the compound of formula (I) with an appropriate acylating agent such as a mixed anhydride or a suitable activated acid, for example an acid halide such as a chloride. Preferably, the reaction is effected in a solvent such as methylene dichloride or tetrahydrofuran, suitably at from around 0° to ambient temperature.

Optional conversation (iv) may be effected by reaction with the appropriate alcohol in the presence of a suitable mineral acid such as sulphuric.

Salts derived from acids include the acetate, adipate, alginate, aspartate, benzoate, benzenesulphonate, bisulphate, butyrate, citrate, camphorate, camphorsulphonate, cyclopentanepropionate, digluconate, dodecylsulphate, ethanesulphonate, fumarate, glucoheptanoate, glycerophos-phate, hemisulphate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulphonate, lactate, maleate, methanesulphonate, 2-naphthalenesulphonate, nicotinate, oxalate, palmoate, pectinate, persulphate, 3-phenyl-propionate, picrate, pivalate, proprionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine and lysine.

Quaternary ammonium salts can be formed where a nitrogen-containing group is present, for example by reaction with lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulphates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides.

Thus, subject to the requirements of novelty and inventive step, according to the present invention we may claim (inter alia):

(a) a compound of formula (I) or an acid addition salt thereof;

(b) a method for preparing a compound of formula (I) or a pharmacologically acceptable acid addition salt thereof;

(c) a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt thereof and a pharmaceutically acceptable carrier therefor;

(d) a method for preparing such formulations;

(e) a method for the inhibition of the lipoxygenase and/or cyclooxygenase pathways of the arachidonic acid metabolism by use of a non-toxic, effective, inhibitory

amount of a compound of formula (I) or a physiologically acceptable salt thereof;

(f) a method for the prophylaxis or treatment of disease in a mammal, including man, comprising the administration to said mammal of a non-toxic, therapeutically or prophylactically effective amount of a compound of formula (I) or a physiologically acceptable salt thereof;

(g) a method for the prophylaxis or treatment of any individual condition described herein, in a mammal, including man, comprising the administration to said mammal of a non-toxic therapeutically or prophylactically effective amount of a compound of formula (I) or a physiologically acceptable salt thereof;

(h) a method for the prophylaxis or treatment of asthma in a mammal, including man, comprising administration to said mammal of a non-toxic, effective, anti-asthmatic amount of a compound of formula (I) or a physiologically acceptable salt thereof;

(i) a compound of formula (I) or a physiologically acceptable salt thereof for use in medicine, especially as defined in (f)–(h) above;

(j) use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of medical therapeutic agents, particularly those for use as defined in (f)–(h) above;

(k) a method of regulating the growth of, or delaying senescence in vegetable matter by application to said matter of an effective amount of a compound of formula (I) or a salt thereof; or

(l) any novel feature described herein.

The following Examples are provided by way of an illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius.

EXAMPLES

Example 1

Preparation of
3-Phenoxy-N-methylcinnamohydroxamic Acid

Methyl chloroformate (2.6 ml) was added dropwise to a solution of m-phenoxycinnamic acid (8 g) and triethylamine (18.5 g) in tetrahydrofuran (60 ml) at 0°. A solution of N-methylhydroxylamine hydrochloride (5.6 g) in water (5 ml) was added, and the mixture was stirred for 2 hours. Isolation with ethyl acetate afforded 3-phenoxy-N-methylcinnamohydroxamic acid (ca 4.3 g), m.pt. 124°–125° [from ethyl acetate/light petroleum (b.pt. 60°–80° C.)]. The m-Phenoxycinnamic acid used as starting material was prepared by condensation of m-phenoxybenzaldehyde with malonic acid in the presence of piperidine and pyridine.

Example 2

Preparation of
2-(2-Fluorobiphenyl-4-yl)-N-methylpropanohydroxamic Acid

2-(2-Fluorobiphenyl-4-yl)propionic acid chloride (prepared in the normal manner from 1.75 g of acid, ca 1 ml of oxalyl chloride, toluene, and 3 drops of N,N-(dimethylformamide) was dissolved in tetrahydrofuran (30 ml) and added over 5–10 minutes to a solution of N-Methylhydroxylamine hydrochloride (ca 2 g) in water (5 ml) containing triethylamine (5 ml) at 0°. Solvent was evaporated, and neutral material was isolated with ethyl acetate. Recrystallization from ether-light petroleum (b.pt. 40°–60°) afforded 2-(2-fluorobiphenyl-4-yl)-N-methylpropanohydroxamic acid (1.25 g), m.pt. 125°–126° C.

Examples 3–24

The following compounds were prepared in a manner generally analogous to the method of Examples 1/2:

(3) 4-(4-Biphenylyl)-N-methyl-4-oxobutanohydroxamic acid, m.pt. 159°–162° C., decomp
(4) N-Methyl-3-(1-naphthyl)propenohydroxamic acid, m.pt. 153°–155° C.
(5) N-Methyl-4-methylcinnamohydroxamic acid, m.pt. 140°–142° C.
(6) 2-Benzyloxy-N-methylcinnamohydroxamic acid, m.pt. 99°–100° C.
(7) N-Methyl-3-trifluoromethylcinnamohydroxamic acid, m.pt. 122°–125° C.
(8) N-Methyl-2-[5-methyl-2-(4-methylphenylcarbamoyl)phenoxyl]acetohydroxamic acid, m.pt. 191°–192° C.
(9) 2-(3-Benzoylphenyl)-N-methylpropionohydroxamic acid, m.pt. 121°–122° C.
(10) 4-(4-Biphenylyloxymethyl)-N-methylbenzohydroxamic acid, m.pt. 104°–105° C.
(11) N-Methyl-4-(3-propoxybenzoyl)benzohydroxamic acid, m.pt. 107°–108° C.
(12) 4-Benzyloxy-N-methylcinnamohydroxamic acid, m.pt. 181°–182° C.
(13) N-Methyl-3-phenoxybenzohydroxamic acid, m.pt. 71°–72° C.
(14) N-Methyl-4-phenoxybenzohydroxamic acid, m.pt. 92°–93° C.
(15) 2-(4-Biphenylyl)-N-methylpropanohydroxamic acid, m.pt. 125°–127° C.
(16) N-Methyl-3-(3-propoxybenzoyl)benzohydroxamic acid, m.pt. 75°–76° C.
(17) N-(Cyclohexyl)-2-[4-(2-methylpropyl)phenyl]-propanohydroxamic acid, m.pt. 133°–135° C.
(18) 3-(4-Biphenylyl)-N-methylpropenohydroxamic acid, m.pt. 198°–199° C. (preheated)
(19) N-Methyl-3-(2-naphthyl)propenohydroxamic acid, m.pt. 150°–151° C.
(20) 2-(2-Fluorobiphenyl-4-yl)-N-cyclohexylpropanohydroxamic acid, m.pt. 195°–196° C.
(21) 2-(2-Fluorobiphenyl-4-yl)-N-t-butylpropanohydroxamic acid, m.pt. 180°–181° C.)
(22) N-(1,1-Dimethylethyl)-3-phenoxycinnamohydroxamic acid, m.pt. 108°–109° C.
(23) 2-(4-Biphenylyloxy)-N-methylpropanohydroxamic acid, m.pt. 166°–167° C.
(24) N-[3-(4-benzyloxyphenyl)prop-2-enyl]acetohydroxamic acid, m.pt. 148°–149° C.
(25) 4-(Biphenyl-4-yloxy)-N-methylbut-2-enohydroxamic acid
(26) 3-(3-Fluoro-4-phenoxyphenyl)-N-methylprop-2-enohydroxamic acid, m.pt. 150°–152° C.

Example 27

Preparation of
N-(4-Benzyloxybenzyl)acetohydroxamic Acid

Sodium cyanoborohydride (21.3 g) was added in portions to a solution of 4-benzyloxybenzaldehyde oxime (51 g) in acetic acid (250 ml) at ca 50° (cooling). After the reduction was complete, acetic anhydride (22.5 ml) was added in one portion, and the mixture was stirred for 1 hour. The mixture was then poured into water, and the neutral product was isolated with ethyl

acetate. The residue was treated with potassium carbonate (2 g) in methanol (400 ml) to hydrolyse the O-acetyl material, then the solvent was evaporated. Addition of 20% citric acid solution (400 ml) and isolation with ethyl acetate furnished N-(4-Benzyloxybenzyl) acetohydroxamic acid (32 g), m.pt. 119°–120° [from ethyl acetate-light petroleum (b.pt. 60°–80°)].

Example 28

Preparation of
N-[4-(2-Pyridyloxy)benzyl]acetohydroxamic Acid

2-Bromopyridine (4.74 g) was added to the sodium salt of 4-methylphenol [from 50% sodium hydride (1.58 g) and the phenol (3.56 g)] in dimethyl sulphoxide, and the mixture was stirred for 20 hours at 150° C. Addition of water, and isolation of non-phenolic material with ether gave the pyridyloxy compound (4.81 g). Without purification, this compound (4.74 g) was refluxed in carbon tetrachloride (125 ml) with N-bromosuccinimide (5.02 g) and azo-bisisobutyronitrile initiator (50 mg). After 1 hour (more initiator added after 15 and 30 minutes), the filtered solution was evaporated in vacuo. The crude product (6.76 g) was immediately stirred with O-(tetrahydropyran-2-yl)hydroxylamine (8.99 g) in N,N-dimethylformamide (65 ml) for 65 hours at room temperature. Addition of water and isolation with ether provided the protected hydroxylamine as a viscous oil. Acetylation of the crude protected hydroxylamine (3.84 g) in methylene dichloride (30 ml) was effected with acetic anhydride (1.44 g) for 2 hours at room temperature. Evaporation of solvent, and isolation of non-acidic material with ether furnished the O-protected hydroxamic acid, which was purified by chromatography over silica gel [elution with 1:1 ethyl acetate/light petroleum (b.pt. 60°–80°)](2.61 g).

A mixture of the O-tetrahydropyranyl hydroxamic acid (2.6 g) and pyridinium p-toluenesulphonate (191 mg) in methanol (25 ml) was refluxed for 9 hours, then evaporated in vacuo. Isolation with ethyl acetate afforded N-[4-(2-pyridyloxy)benzyl]acetohydroxamic acid (1.42 g), m.pt. 97°–99° C. after recrystallization from ethyl acetate-light petroleum (b.pt. 60°–80°).

Examples 29–69

The following compounds were prepared in a manner generally analogous to the method of Examples 27 and 28:

(29) N-[2-(2-Naphthyloxy)ethyl]benzohydroxamic acid, m.pt. 163°–165° C.
(30) N-[2-(5,6,7,8-Tetrahydro-2-naphthyloxy)ethyl]-acetohydroxamic acid, m.pt. 73°–74° C.
(31) N-[1-(4-Biphenylyl)ethyl]acetohydroxamic acid, m.pt. 143°–153° C., vague m.pt.
(32) N-[1-(4-Benzyloxy-2-hydroxyphenyl)ethyl-]acetohydroxamic acid, m.pt. 149°–150° C.
(33) N-(2-Benzyloxybenzyl)acetohydroxamic acid, oil
(34) N-(3-Benzyloxybenzyl)acetohydroxamic acid, m.pt. 95°–98° C.
(35) N-(3-Phenoxylbenzyl)acetohydroxamic acid, m.pt. 81°–82° C.
(36) N-(4-Biphenylylmethyl)acetohydroxamic acid, m.pt. 152°–155° C.
(37) N-[4-(1-Naphthylmethoxy)benzyl]acetohydroxamic acid, m.pt. 127°–130° C.
(38) N-[4-(2-Naphthylmethoxy)benzyl]acetohydroxamic acid, m.pt. 161°–14° C.
(39) N-(4-Phenoxybenzyl)acetohydroxamic acid, m.pt. 116°–119° C.
(40) N-(4-Benzyloxybenzyl)pivalohydroxamic acid, m.pt. 143°–144° C.
(41) 2-(2-Fluoro-4-biphenylyl)-N-isopropylpropanohydroxamic acid, m.pt. 151°–152° C.
(42) N-(4-Benzyloxybenzyl)-2-methylpropanohydroxamic acid, m.pt. 113°–115° C.
(43) N-(4-Phenylcarbamoylbenzyl)acetohydroxamic acid, m.pt. 194°–196° C.
(44) N-[(2',4'-Difluoro-4-biphenylyl(methyl]acetohydroxamic acid, m.pt. 134°–135° C.
(45) N-[1-(2',4'-Difluoro-4-biphenylyl)ethyl]-2,2-dimethylpropanohydroxamic acid, m.pt. 152°–153° C.
(46) N-[4-(4-Biphenylylmethoxy)benzyl]acetohydroxamic acid, m.pt. vague, softens 165° C. melts 175° C.
(47) N-[4-(2,4-Difluorobenzyloxy)benzyl]acetohydroxamic acid, m.pt. 113°–115° C.
(48)N-[4-(2,4-Difluorobenzyloxy)benzyl]pivalohydroxamic acid, m.pt. 134°–136° C.
(49) N-[5,6,7,8-Tetrahydro-2-naphthyl)methyl]acetohydroxamic acid, m.pt. 79°–81° C.
(50) N-[2-(5,6,7,8-Tetrohydro-2-naphthyloxy)ethyl]-pivalohydroxamic acid, m.pt. 85°–87° C.
(51) N-(5,6,7,8-Tetrahydro-2-naphthylally]acetohydroxamic acid, softens, 95° C. melts, 106°–107° C.
(52) N-(5,6,7,8-Tetrahydro-2-naphthylallyl)pivalohydroxamic acid, m.pt. 144°–145° C.
(53) N-(5,6,7,8-Tetrahydro-2-naphthylmethyl)pivalohydroxamic acid, m.pt. 103°–105° C.
(54) N-[2-(2',4'-Difluoro-4-biphenylyl)ethylacetohydroxamic acid, m.pt. 122°–123° C.
(55) N-(4-Isobutylbenzyl)acetohydroxamic acid, m.pt. 89°–90° C.
(56) N-[1-(4-Biphenyl)ethyl]pivalohydroxamic acid, m.pt. 170°–171° C.
(57) N-[(4-Biphenylyl)methyl]pivalohydroxamic acid, m.pt. 164°–165° C.
(58) N-(3-Phenoxycinnamyl)acetohydroxamic acid, light brown oil
(59) N-[2-(4-Biphenylyloxy)ethyl]acetohydroxamic acid, m.p.t. 125°–127° C.
(60) N-[3-(4-Benzyloxyphenyl)prop-2-enyl]acetohydroxamic acid, m.pt. 148°–149° C.
(61) N-[4-(2-Pyridyl)benzyl]acetohydroxamic acid, m.pt. 134°–135° C. (softens ca 125° C.)
(62) N-[4-(2,4-Difluorophenoxymethyl)benzyl]acetohydroxamic acid, m.pt. 112°–113° C.
(63) N-[4-(2-Pyridyloxy)benzyl]acetohydroxamic acid, m.pt. 97°–99° C.
(64) N-(5-Phenoxymethyl-2-thienylmethyl)acetohydroxamic acid, m.pt. 103°–104° C.
(65) 3-(4-Fluoro-3-phenoxyphenyl)-N-methylprop-2-enohydroxamic acid, m.pt. 150°–152° C.
(66) N-(6-Phenoxy-2-pyridylmethyl)acetohydroxamic acid
(67) N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl-]acetohydroxamic acid
(68) N-[4-(Benzylthio)benzyl]acetohydroxamic acid
(69) N-[3-(2-Pyridyloxy)benzyl]acetohydroxamic acid

Example 70

Preparation of
5-[2-(4-Biphenylyl)ethyl]-1-hydroxy-2-pyrrolidinone

Methyl-1-(4-biphenylyl)-2-oxobutanoate (1.48 g) in ethanol (40 ml) with hydroxylamine hydrochloride (0.348 g) and sodium acetate (0.41 g) was stirred for 16

hours at ambient temperature. Dilution with water precipitated the oxime (1.368 g) which was dissolved (without purification) in acetic acid (15 ml) and treated with sodium cyanoborohydride (0.41 g) under nitrogen. The mixture was stirred for 3 hours at room temperature, then non-acidic material was isolated with ethyl acetate. The resulting crude hydroxylamine in toluene (25 ml) containing p-toluenesulphonic acid catalyst (80 mg) was heated for 1.25 hours at 100° to precipitate 5-[2-(4-Biphenylyl)ethyl]-1-hydroxy-2-pyrrolidinone (0.875 g), m.pt. 192°–194° C. after recrystallization from methanol.

Examples 71–75

The following compounds were prepared in a manner generally analogous to that described in Example 70:

(71) 1-Hydroxy-5-[2-(2-naphthyl)ethyl]pyrrolidin-2-one, m.pt. 163°–164° C.

(72) 5-(4-Biphenylyl)-1-hydroxy-2-pyrrolidone, decomp. at 195° C. in preheated apparatus

(73) 1-Hydroxy-5-(2-phenylethyl)-2-pyrrolidinone m.pt. 120°–122° C.

(74) 1-Hydroxy-5-(3-phenylpropyl)-2-pyrrolidinone m.pt. 63°–65° C.

(75) 5-[2-(4-Benzyloxyphenyl)ethyl]-1-hydroxy-2-pyrrolidone, m.pt. 155°–157° C.

Example 76

Preparation of
5,6-Dihydro-1-hydroxy-5-(1-naphthyl)-1,4-thiazin-3(2H, 4H)-one

A solution of methyl mercaptoacetate (2.3 g) in tetrahydrofuran (15 ml) was added dropwise to 1-(1-Naphthyl)-2-nitroethene (4.32 g) and triethylamine (0.219 ml) in tetrahydrofuran (100 ml). The mixture was stirred for 30 minutes at room temperature, then evaporated in vacuo. The residue (6.12 g) was dissolved in saturated aqueous ammonium chloride solution (120 ml) and 95% ethanol (to give homogeneous solution), then stirred while powdered zinc (2.62 g) was added. The mixture was stirred for 30 minutes at room temperature, then concentrated. Isolation with ethyl acetate furnished 5,6-Dihydro-1-hydroxy-5-(1-naphthyl)-1,4-thiazine-3(2H, 4H)-one (2.09 g), m.pt. 155°–157° C. after recrystallization from ethyl acetate.

Examples 77–80

The following compounds were prepared in a manner generally analogous to that described in Example 76:

(77) 5,6-Dihydro-N-hydroxy-phenyl-1,4-thiazin-3(2H, 4H)-one, m.pt. 159°–160° C.

(78) 6-(4-Biphenylyl)-5,6-dihydro-4-hydroxy-1,4-thiazin-3-(2H, 4H)-one, m.pt. 198°–201° C.

(79) 5,6-Dihydro-4-hydroxy-6-(2-naphthyl)-1,4-thiazin-3(2H, 4H)-one, m.pt. 184°–86° C.

(80) 6-(4-Benzyloxyphenyl)-5,6-dihydro-4-hydroxy-1,4-thiazin-3(2H, 4H)one, m.pt. 179°–181° C.

Example 81

Preparation of
1-Hydroxy-1-[2-(2-naphthyloxy)ethyl]-3-phenylurea

A mixture of 2-naphthyloxyacetaldehyde hydrate (9.85 g), benzyloxyamine (5.94 g) and ethanol (100 ml) was stirred overnight under nitrogen to precipitate 11.21 g of the protected oxime, m.pt. 68°–69.5° C. The oxime (10.1 g) in acetic acid (100 ml) was reduced with sodium cyanoborohydride, then the isolated O-benzyl hydroxylamine, without purification, was treated with phenyl isocyanate (1 equivalent) in toluene for 4 hours at 110° C. The product had m.pt. 75°–77° C. after chromatography over silica gel (elution with methylene chloride) and recrystallization from SVM. Hydrogenation of the last-mentioned O-benzylhydroxyurea over 5% palladium on charcoal in ethanol containing a few drops of acetic acid provided 1-Hydroxy-1-[2-(2-naphthyloxy)ethyl]-3-phenylurea, m.pt. 165°–167° C. (from ethanol).

Example 82

Preparation of
N-(4-Benzyloxybenzyl)-N-hydroxy-N-methylurea

Sodium cyanoborohydride (1.94 g) was added to 4-Benzyloxybenzaldoxime (3.5 g) in acetic acid (30 ml) under N_2, and the mixture was stirred overnight at room temperature. Solvent was evaporated, and the product (4 g) was isolated with ether. Methyl isocyanate (0.88 g) in ether (10 ml) was added dropwise to a solution of the crude hydroxylamine in toluene (100 ml) at 0°, and the mixture was stirred for 3 hours at room temperature to precipitate N-(4-Benzyloxybenzyl)-N-hydroxy-N'-methylurea (2.2 g), m.pt. 152°–154° after recrystallization from ethyl acetate-light petroleum (m.pt. 60°–80°).

Examples 83–91

The following compounds were prepared in a manner generally analogous to that described in Examples 81 and 82:

(83) N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-methylurea

(84) N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-t-butylurea

(85) N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-cyclohexylurea

(86) N-[3-(4-Fluoro-3-phenoxyphenyl)prop-2-enyl]-N-hydroxy-N'-phenylurea

(87) N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-methylurea

(88) N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-t-butylurea

(89) N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-cyclohexylurea

(90) N-(Biphenyl-4-ylmethyl)-N-hydroxy-N'-phenylurea

(91) N-Hydroxy-N'-methyl-N-[3-(2-pyridyloxy)benzyl]urea

Example 92

Preparation of
3-(4-Benzyloxybenzyl)-1,3-dihydro-1-hydroxyimidazol-2-one

A mixture of 4-benzyloxybenzaldehyde (9.1 g), aminoacetaldehyde diethyl acetal (6.9 g) and p-toluenesulphonic acid (0.5 g) in toluene (250 ml) as refluxed through a Dean-Stark trap until ca 1 ml of water had been collected. Solvent was evaporated in vacuo, and the crude imine was dissolved in acetic acid (100 ml). Sodium cyanoborohydride (3.15 g) was added in portions under nitrogen, and the mixture was stirred until the reaction was complete. Solvent was evaporated in vacuo, and the amine was isolated free of acidic material with ethyl acetate.

To the crude amine (14.15 g) with triethylamine (14 ml) in toluene (40 ml) was added to 12% phosgene in toluene solution (250 ml) to −40°, and the mixture was warmed to room temperature over 1 hour. Solvent was evaporated, and material soluble in ether was dissolved in tetrahydrofuran (150 ml) and treated with triethylamine (25 ml), hydroxylamine hydrochloride (11 g) and water (25 ml). The mixture was stirred for 1 hour, and evaporated in vacuo.

The crude hydroxyurea was isolated with ethyl acetate, then (18 g) dissolved in chloroform (50 ml) and treated with trifluoroacetic acid (25 ml) and water (25 ml). After 1 hour, the precipitated solid was collected and recrystallized from ethanol/N,N-dimethylformamide to give 3-(4-Benzyloxybenzyl)-1,3-dihydro-1-hydroxyimidazol-2-one (6 g) which darkens without melting at greater than 175°.

Examples 93–85

The following compounds were prepared in a manner generally analogous to that described in Example 92:

(93) 1,3-Dihydro-1-hydroxy-3-(4-phenylbenzyl-)imidazol-2-one, softens 180° gradually decomposed at to 220° C.

(94) 1-Hydroxy-3-(3-phenoxybenzyl)-1,3-dihydroimidazol-2-one

(95) 1-Hydroxy-3-(6-phenoxy-2-pyridylmethyl)-1,3-dihydroimidazol-2-one

Example 96

Preparation of N-(4-Benzyloxybenzyl)-O-methylcarbamoylacetohydroxamic Acid

A mixture of N-(4-benzyloxybenzyl)acetohydroxamic acid (1.35 g), methyl isocyanate (0.65 g) and 1,8-diazabicyclo [5.4.0] undec-7-ene catalyst (1 drop) in tetrahydrofuran (10 ml) was stirred for 3 hours then left overnight to provide N-(4-benzyloxybenzyl)-O-methylcarbamoylacetohydroxamic acid (1.35 g) m.pt. 101°–102° [from ethyl acetate-light petroleum (b.pt. 60°–80°)].

Example 97–99

The following compounds were prepared in a manner generally analogous to that described in Example 96:

(97) N-[2-(2-Naphthylthio)ethyl]-N-(phenylcarbamoyloxy)acetamide, m.pt. 96°–98° C.

(98) N-[4-(Benzyloxybenzyl)-O-(methylcarbamoyl)-pivalohydroxamic acid, m.pt. 135°–136° C.

(99) N-(4-Benzyloxybenzyl)-O-(2,2-dimethylethyl)carbamoylacetohydroxamic acid, m.pt. 82°–83° C.

Example 100

Preparation of N-(4-Benzyloxybenzyl)-N-(t-butylcarbonyloxy)acetamide

Pivaloylchloride (1.36 ml) was added dropwise to a solution of N-(4-benzyloxybenzyl)acetohydroxamic acid (2.71 g) and triethylamine (1.7 ml) in methylene dichloride (15 ml) and dimethylaminopyridine (100 ml). The mixture was stirred for 2 hours at room temperature, then neutral material was isolated with ether. The product, N-(4-Benzyloxybenzyl)-N-(t-butylcarbonyloxy)acetamide, was a colourless oil.

Example 101

3-[N-(4-Benzyloxybenzyl)acetamidooxycarbonyl]-propanoic acid, m.pt. 102°–105° was prepared in a manner generally analogous to that described in Example 100.

Example 102

Preservation of Cut Flowers

The compound of Example 27 was made up as a 1 mM solution and the cut stem ends of cut carnations were immersed in the resultant solution in order to prolong their freshness.

Pharmaceutical Formulations

In the following formulation Examples, the "Active Ingredient" may be any compound of formula (I) or a physiologically acceptable salt thereof, for example the compound of Example 27.

EXAMPLE A

Tablet

	In one tablet
Active Ingredient	5.0 mg
Lactose	82.0 mg
Starch	10.0 mg
Povidone	2.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, lactose and starch. Granulate the powders using a solution of povidone in purified water. Dry the granules, add the magnesium stearate and compress to produce tablets, 100 mg per tablet.

EXAMPLE B

Ointment

Active Ingredient	1.0 g
White Soft Paraffin	to 100.0 g

Disperse the active ingredient in a small volume of the vehicle. Gradually incorporate this into the bulk to produce a smooth, homogeneous product. Fill into collapsible metal tubes.

EXAMPLE C

Cream for Topical Use

Active Ingredient	1.0 g
Polawax GP 200	20.0 g
Lanolin Anhydrous	2.0 g
White Beeswax	2.5 g
Methyl Hydroxybenzoate	0.1 g
Distilled Water	to 100.0 g

Heat the Polawax, beeswax and lanolin together at 60° C. Add a solution of methyl hydroxybenzoate. Homogenise using high speed stirring. Allow the temperature to fall to 50°. Add and disperse the active ingredient. Allow to cool with slow speed stirring.

EXAMPLE D

Lotion for Topical Use

Active Ingredient	1.0 g
Sorbitan Monolaurate	0.6 g
Polysorbate 20	0.6 g
Cetostearyl Alcohol	1.2 g
Glycerin	6.0 g
Methyl Hydroxybenzoate	0.2 g
Purified Water B.P.	to 100.00 ml

The methyl hydroxybenzoate and glycerin were dissolved in 70 ml of the water at 75° C. The sorbitan monolaurate, Polysorbate 20 and cetostearyl alcohol were melted together at 75° C. and added to the aqueous solution. The resulting emulsion was homogenised, allowed to cool with continuous stirring and the active ingredient added as a suspension in the remaining water. The whole was stirred until homogeneous.

EXAMPLE E

Eye Drops	
Active Ingredient	0.5 g
Methyl Hydroxybenzoate	0.01 g
Propyl Hydroxybenzoate	0.04 g
Purified Water B.P.	to 100.00 ml

The methyl and propyl hydroxybenzoates were dissolved in 70 ml purified water at 75° and the resulting solution then allowed to cool. The active ingredient was added next and the solution made up to 100 ml with purified water. The solution was sterilised by filtration through a membrane filter 0.22μ pore size and packed aseptically into suitable sterile containers.

EXAMPLE F

Injection Solution	
Active Ingredient	10.0 mg
Water for Injections B.P.	to 1.0 ml

The active ingredient was dissolved in half of the Water for Injections and then made up to volume and sterilised by filtration. The resulting solution was distributed into ampoules under aseptic conditions.

Pulmonary Formulations

In formulations G and H below, the "Active Ingredient" may be any compound of formula (I) or physiologically acceptable salt thereof, for example the compound of Example 1.

EXAMPLE G

Powder Capsules for Inhalation	
Active Ingredient (0.5–7.0 μm powder)	4 mg
Lactose (30–90 μm powder)	46.0 mg

The powders were mixed until homogeneous and filled into suitably sized hard gelatin capsules, 50 mg of mixture per capsule.

EXAMPLE H

Inhalation Aerosol	
Active Ingredient (0.5–7.0 μm powder)	200 mg
Sorbitan Trioleate	100 mg
Saccharin Sodium (0.5–7.0 μm powder)	2 mg
Methanol	2 mg
Trichlorofluoromethane	4.2 g
Dichlorodifluoromethane	to 10.0 ml

The Sorbitan Trioleate and Menthol were dissolved in the Trichlorofluoromethane. The Saccharin Sodium and active ingredient were dispersed in the mixture which was then transferred to a suitable aerosol canister and the Dichlorofluoromethane injected through the valve system. This composition provides 2 mg of active ingredient in each 100 μl dose.

In vitro inhibition of 5-lipoxygenase (LO) and Cyclooxygenase (CO)

Blood from normal aspirin-free volunteers was centrifuged to separate leukocytes from red cells and platelets. The leukocytes were homogenised and 5 μM arachidonic acid added, followed by incubation at 37° for 5 minutes. The reaction was stopped by boiling. Radioimmunoassay was conducted for leukotriene B_4 (an LO product) and thromboxane B_4 (a CO product). Results were calculated as IC_{50} μM activity against each enzyme and as listed below.

	Activity (μM)	
Compound Example No.	CO	LO
1	3.0	<0.1

We claim:

1. N-(3-phenoxycinnamyl)acetohydroxamic acid.

2. A salt of N-(3-phenoxycinnamyl)acetohydroxamic acid.

3. A physiologically acceptable salt of N-(3-phenoxycinnamyl)acetohydroxamic acid.

4. A pharmaceutical composition comprising N-(3-phenoxycinnamyl)acetohydroxyamic acid or a physiologically acceptable salt thereof together with a physiologically acceptable carrier therefor.

5. A method of inhibiting lipoxigenase and cyclooxygenase enzymes in a mammal which comprises administering an effective inhibition amount of N-(3-phenoxycinnamyl)acetohydroxamic acid or a physiologically acceptable salt thereof to said mammal.

6. The method of claim 5 in which the mammal is a human.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,738,986

DATED : April 19, 1988

INVENTOR(S) : Geoffrey Kneen, William P. Jackson, Peter J. Islip and Peter J. Wates

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, lines 31 to 36; the formula should appear as follows:

Column 4, lines 27 to 32; the formula should appear as follows:

Column 17, lines 28 to 33; the formula should appear as follows:

Signed and Sealed this

Twenty-eighth Day of May, 1991

Attest:

Attesting Officer

HARRY F. MANBECK, JR.

Commissioner of Patents and Trademarks

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,738,986

DATED : April 19, 1988

INVENTOR(S) : Geoffrey Kneen, William P. Jackson, Peter J. Islip and Peter J. Wates

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the abstract, lines 50 to 56; the formula should appear as follows:

Exhibit B

United States Patent [19]

Lafon

[11] Patent Number: 4,713,395

[45] Date of Patent: Dec. 15, 1987

[54] ACETOHYDROXAMIC ACID DERIVATIVE

[75] Inventor: Louis Lafon, Paris, France

[73] Assignee: Societe Anonyme Dite: Laboratoire L. LaFon, Maisons Alfort, France

[21] Appl. No.: 890,561

[22] Filed: Jul. 30, 1986

[30] Foreign Application Priority Data

Jul. 31, 1985 [FR] France 85 11685

[51] Int. Cl.[4] A61K 31/04; A61K 31/085; A61K 31/185; C07C 83/10

[52] U.S. Cl. ..... 514/575; 260/500.5 H

[58] Field of Search ..... 260/500.5 H; 514/575

[56] References Cited

U.S. PATENT DOCUMENTS

3,787,569	1/1974	Johnson et al.	514/575
4,083,996	4/1978	Tanaka et al.	514/575

Primary Examiner—J. E. Evans

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] ABSTRACT

The present invention relates, by way of a new industrial product, to an acetohydroxamic acid derivative, namely 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid.

This product is useful in therapy, in particular as a sedative.

It can be prepared by reacting NH_2OH with a C_1–C_3 lower alkyl 5-chloro-4-nitro-2-methoxybenzamidoacetate.

3 Claims, No Drawings

ACETOHYDROXAMIC ACID DERIVATIVE

The present invention relates, by way of a new industrial product, to an acetohydroxamic acid derivative, namely 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid. It also relates to the method for its preparation and its use in therapy, in particular as a sedative.

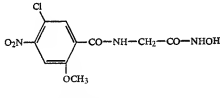
Patent Document BE-A-No. 852 738 has disclosed 2-(4-aminobenzamido)acetohydroxamic acid hydrochloride, which has the Code no.: CRL 40 473 and has effects on the central nervous system (see Example 18 of the said Belgian patent). 3-(3-Aminobenzamido)propionohydroxamic acid hydrochloride, which has the Code no.: CRL 40 816 and has particularly valuable antidepressant properties, is also known.

It has now been found, surprisingly, that the new compound according to the invention, namely 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid (Code no.: CRL 40 636), which is structurally different from the known products mentioned above, is particularly valuable in therapy on account of its effects on the central nervous system (CNS).

Briefly, CRL 40 636 according to the invention is noteworthy for its sedative effects, whereas (i) CRL 40 473 has moderate sedative and antidepressant effects and (ii) CRL 40 816 is more an antidepressant than a sedative.

The results of comparative tests recorded in Table I below show that CRL 40 636 (product of Example 1 according to the invention) is more active and acts at lower doses than CRL 40 473 (comparison product CP-1) and CRL 40 816 (comparison product CP-2) mentioned above, according to the so-called intergroup aggressiveness test.

A therapeutic composition recommended according to the invention contains, in association with a physiologically acceptable excipient, 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid of the structural formula:

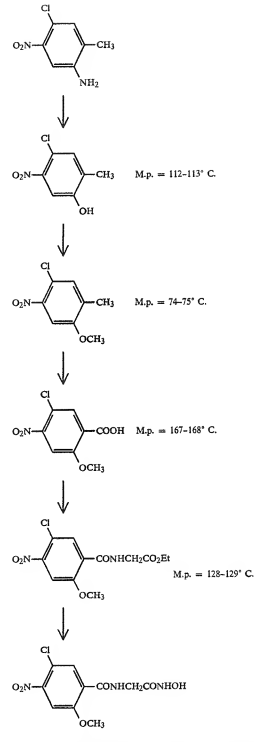


(I)

The compound according to the invention can be prepared using a method known per se by the application of conventional reaction mechanisms. The method recommended here consists in reacting hydroxylamine with a C_1–C_3 lower alkyl 5-chloro-4-nitro-2-methoxybenzamidoacetate at room temperature (15°–20° C.) for at least 1 hour, preferably for at least 4 hours, in proportions of 1 to 1.1 mol of NH_2OH per mol of alkyl 5-chloro-4-nitro-2-methoxybenzamidoacetate.

The total synthesis of the product of the invention, starting from 5-nitro-4-chloro-2-methylaniline, is illustrated by diagram A below.

DIAGRAM A



Further advantages and characteristics of the invention will be understood more clearly from the following description of a preparative example on the one hand and results of neuropsychopharmacological tests on the other. Of course, these data as a whole do not in any way imply a limitation but are given by way of illustration.

EXAMPLE 1

Preparation of
2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid

(Code no.: CRL 40 636)

A solution of hydroxylamine is prepared with 5.6 g (0.08 mol) of hydroxylamine hydrochloride and 3.68 g (0.16 g at) of sodium in 250 ml of methanol. 23.8 g (0.075 mol) of ethyl 5-chloro-4-nitro-2-methoxybenzamidoacetate are added and the ingredients are left in contact overnight. The sodium salt is filtered off, washed with methanol and dried. The dried product thus obtained is taken up in 200 ml of water, the mixture is filtered and the filtrate is precipitated with 3N HCl. The precipitate is filtered off, washed with water and dried. Recrystallization from a C_2H_5OH/H_2O mixture (96:4 by weight) gives CRL 40 636 with a yield of 44%. M.p. = 196°-198° C. (with decomposition).

The results of the tests which were undertaken with the compound according to the invention have been summarized below. In the present neuropsychopharmacological study, a suspension of CRL 40 636 in an aqueous solution of gum arabic was administered intraperitoneally in a volume of 20 ml/kg to male mice and 5 ml/kg to male rats.

I. TOXICITY

CRL 40 636 is not toxic. In fact, in mice, the LD_0 (maximum non-lethal dose) by intraperitoneal administration is greater than 1024 mg/kg.

II. OVERALL BEHAVIOR AND REACTIVITIES

Groups of three animals are observed before and then 0.25 hour, 0.50 hour, 1 hour, 2 hours, 3 hours and 24 hours after the administration of CRL 40 636. The following observations are made:

(1°) in mice

at a dose of 512 mg/kg:
- sedation with a decrease in the fear and aggressiveness reactions, the muscular strength and the reactivity to touch for 3 hours,
- hypothermia (−6.8° C.) for more than 3 hours, and
- depressed respiration for 2 to 3 hours;

at a dose of 128 mg/kg:
- sedation with a decrease in the fear and aggressiveness reaction for 3 hours,
- hypothermia (−3.1° C.) for 2 hours, and
- depressed respiration for 2 to 3 hours;

at a dose of 32 mg/kg:
- sedation (2 out of 3 animals) for 3 hours,
- moderate hypothermia (−2.2° C.) for 1 hour, and
- depressed respiration (2 out of 3 animals) for 2 hours; and

at a dose of 8 mg/kg:
- variable sedation (2 out of 3 animals) for 0.5 to 1 hour; and

(2°) in rats

at a dose of 256 mg/kg:
- sedation for 24 hours with a decrease in the muscular strength and tonus for 1 to 3 hours,
- mydriasis for 2 hours, and
- depressed respiration for 1 to 3 hours;

at a dose of 64 mg/kg:
- sedation for 1 to 3 hours with a decrease in the muscular strength and tonus, and
- depressed respiration for 1 hour;

at a dose of 16 mg/kg:
- sedation (0.25 to 1 hour) with a decrease in the muscular strength and tonus, and
- depressed respiration for 0.25 to 1 hour; and

at a dose of 4 mg/kg:
- sedation for 0.25 to 0.50 hour accompanied by muscular hypotonia, and
- depressed respiration for 0.25 hour.

III. INTERACTION WITH APOMORPHINE

(1°) In mice

Half an hour after the administration of CRL 40 636, groups of 6 mice receive a subcutaneous injection of apomorphine at a dose of 1 or 16 mg/kg. It is found that, at doses of 128 and 512 mg/kg, CRL 40 636 (which exerts a significant hypothermic effect when administered by itself) does not oppose the hypothermia, the righting attitude or the stereotypies induced by apomorphine in mice.

(2°) In rats

Apomorphine is injected subcutaneously at a dose of 0.5 mg/kg into groups of 6 rats 0.5 hour after the administration of CRL 40 636. It is observed that the stereotypies induced by apomorphine in rats are not modified by CRL 40 636.

IV. INTERACTION WITH AMPHETAMINE

0.5 hour or 1 hour after the administration of CRL 40 636, groups of 6 rats receive an intraperitoneal injection of 2 mg/kg of amphetamine.

It is found that, as from a dose of 4 mg/kg, CRL 40 636 strongly antagonizes the stereotypies induced by amphetamine (whereas CRL 40 816, mentioned above, only causes a moderate decrease in the said stereotypies as from a dose of 256 mg/kg i.p.); it is also observed that, although the antagonism of these stereotypies by CRL 40 636 is very intense initially, it seems to disappear rapidly.

V. INTERACTION WITH RESERPINE

Four hours after the administration of reserpine (2.5 mg/kg), groups of 6 mice receive CRL 40 636. It is found that CRL 40 636 does not modify the hypothermia or the ptosis induced by reserpine.

VI. INTERACTION WITH OXOTREMORINE

Oxotremorine (0.5 mg/kg) is injected intraperitoneally into groups of 6 mice half an hour after the administration of CRL 40 636. It is observed that CRL 40 636, which exerts a significant hypothermic effect at doses of 32, 128 and 512 mg/kg, does not oppose, at these doses, the hypothermia induced by oxotremorine, that it is devoid of any effect on the trembling caused by oxotremorine, but that it seems to prolong lachrymation (implying an action on the peripheral cholinergic symptoms).

VII. ACTION ON THE FOUR PLATE TEST, TRACTION AND ELECTRIC SHOCK

The test is performed on groups of 10 mice half an hour after the administration of CRL 40 636. It is found that CRL 40 636 does not cause an increase in the number of punished passes, that, at a high dose, it causes motor incapacity in 30% of the animals, and that it does not modify the convulsant and lethal effects of electric shock.

VIII. ACTION ON THE SPONTANEOUS MOTILITY

Half an hour after they have received CRL 40 636, the mice (6 per dose, 12 control animals) are placed in an actimeter, where their motility is recorded for 0.5 hour. It is found that, at doses of 128 and 512 mg/kg, CRL 40 636 causes a significant decrease in the spontaneous motility, whereas CRL 40 816, mentioned above, only causes a moderate decrease in the said motility at a dose of 512 mg/kg.

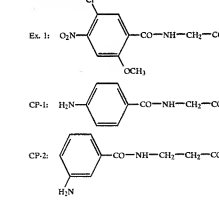
IX. ACTION ON THE INTERGROUP AGGRESSIVENESS (comparative study)

After they have stayed for 3 weeks in the two halves of a cage divided by an opaque partition, groups of 3 male mice (each mouse weighing about 20 g) receive the products to be tested, namely CRL 40 636 (Example 1), CRL 40 473 (CP-1) and CRL 40 816 (CP-2), by intraperitoneal administration in an aqueous solution of gum arabic, at a rate of three cages per product and per dose and six cages for the control animals receiving only the aqueous solution of gum arabic by intraperitoneal administration. Half an hour later, the two groups from the same cage are brought together and the number of fights which occur in 10 minutes is noted. The results are collated in Table I below and show that CRL 40 636 according to the invention (i) greatly decreases the number of fights at a dose of 64 mg/kg, (ii) totally eliminates fights at a dose of 128 mg/kg, and (iii) has a beneficial antiaggressive effect which is considerably greater than that of CRL 40 473 according to Example 18 of the abovementioned Belgian patent, on the one hand, and that of CRL 40 816, on the other.

TABLE I

		Comparative tests			
Product	Code No.	Dose (mg/kg)	Number of fights per mouse	Decrease in the number of fights compared with the control animals
control animals	—	—	3.05	0%
Ex. 1	CRL 40 636	64	1.48	51%
Ex. 1	CRL 40 636	128	0	100%
CP-1	CRL 40 473	128	1.80	40%
CP-1	CRL 40 473	512	2.23	26%
CP-2	CRL 40 816	128	1.42	53%
CP-2	CRL 40 816	512	0	100%

Note:
structural formulae of the products



X. ACTION TOWARDS SOME FORMS OF BEHAVIOR PERTURBED BY VARIOUS AGENTS

(1°) Motility reduced by habituation to the enclosure

After they have stayed in the actimeters for 18 hours, the mice (6 per dose, 12 control animals) receive CRL 40 636. They are immediately returned to their respective enclosures and, half an hour later, their motility is recorded for 30 minutes.

It is observed that CRL 40 636 does not cause a distinct resumption in the motor activity of mice accustomed to their enclosure.

(2°) Motility reduced by hypoxic aggression

Half an hour after they have received CRL 40 636, the mice (10 per dose, 20 control animals) are subjected to acute hypobaric anoxia [pressure reduction of 600 mm Hg (i.e. about 8×10^4 Pa) in 90 seconds; release of vacuum in 45 seconds] and are then placed in an actimeter, where their motility is recorded for 10 minutes.

It is observed that CRL 40 636 does not cause a distinct improvement in the motor recovery of mice whose motility has been depressed following a brief period in a reduced-pressure enclosure.

(3°) Asphyxiant anoxia

Groups of 10 mice receive CRL 40 636 half an hour before the intraperitoneal administration of 32 mg/kg of gallamine triiodoethylate (reference curarizing agent).

It is observed that CRL 40 636 does not modify the time taken for convulsions and death to occur following asphyxiant anoxia caused by a curarizing agent.

XI. COMPLEMENTARY TEST

A complementary test was performed with the product according to the invention, the latter being administered gastrically, as a suspension in an aqueous solution of gum arabic, in a volume of 5 ml/kg, to groups of 6 male rats 0.5 hour or 1 hour before the intraperitoneal administration of 2 mg/kg of amphetamine.

It is found that CRL 40 636 briefly antagonizes the stereotypies induced by amphetamine in rats.

XII. CONCLUSIONS

The results of the tests given above show that CRL 40 636 exhibits, in its neuropsychopharmacological profile, very intense, essentially sedative effects demonstrated by hypomotility, hypothermia, a decrease in the reactivities and a decrease in the intergroup aggressiveness, and that it is practically devoid of antidepressant effects (no antagonism of the hypothermia induced by apomorphine, reserpine and oxotremorine).

In clinical trials on adult humans, CRL 40 636 was shown to be an excellent sedative when administered orally at a daily dose of 50 to 100 mg. The dosage to be administered consists especially of two to four tablets or gelatine capsules per day, each containing 25 mg of CRL 40 636.

The use of 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid is recommended for obtaining a sedative drug intended for therapeutic purposes in patients requiring a drug of this kind, especially in cases of overexcitement.

What is claimed is:

1. 2-(5-Chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid.

2. A therapeutic composition comprising, in association with a physiologically acceptable excipient, a pharmaceutically effective amount of 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid according to claim 1.

3. A method for treating a patient suffering from overexcitement, which comprises administering to such a patient a pharmaceutically effective amount of 2-(5-chloro-4-nitro-2-methoxybenzamido)acetohydroxamic acid according to claim 1.

* * * * *

Exhibit C

United States Patent [19]

Copp et al.

[11] Patent Number: 4,465,685

[45] Date of Patent: Aug. 14, 1984

[54] **ANTIINFLAMMATORY PYRAZOLE THIOUREAS**

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[73] Assignee: Burroughs Wellcome Co., Research Triangle Park, N.C.

[21] Appl. No.: 331,011

[22] Filed: Dec. 15, 1981

[30] Foreign Application Priority Data

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[52] U.S. Cl. ..... 424/258; 424/263; 424/266; 424/273 P; 546/153; 546/159; 546/162; 546/163; 546/256; 546/279; 548/362

[58] Field of Search ..... 548/362; 546/153, 159, 546/163, 256, 279, 162; 424/258, 263, 266, 273 P

[56] References Cited

U.S. PATENT DOCUMENTS

3,646,059 2/1972 Brantley 548/362

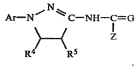
OTHER PUBLICATIONS

Duffin et al., J. Chem. Soc., 1954, pp. 408–415.

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—Donald Brown

[57] ABSTRACT

Compounds of formula (I)



(I)

inhibit both the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid oxygenation and are useful in medicine as, e.g., anti-inflammatory and anti-asthmatic agents.

The compounds may be administered as the raw chemical or in association with a carrier as a pharmaceutical formulation.

The compounds may be prepared by methods analogous to those known in the art, e.g. by the method of Duffin and Kendall in J. Chem. Soc. (1954), 408–415, or by other methods.

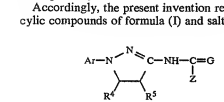
21 Claims, No Drawings

ANTIINFLAMMATORY PYRAZOLE THIOUREAS

This invention relates to formulations comprising heterocylic compounds and their preparation, to their use in medicine in a mammal, including man, e.g. as anti-inflammatory or anti-allergic agents or as agents in the prevention of tissue rejection, and to certain novel heterocylic compounds and their preparation.

In their studies on the reaction of diazonium salts with 1-aryl-2-pyrazolines Duffin and Kendall (J. Chem. Soc., (1954), 408–415) produced 3-(N^2-phenylthioureido)-1-phenyl-2-pyrazoline (page 409 and 413) in tests on the product of an earlier reaction. It has now been found that compounds in which the phenyl ring is substituted and other compounds of formula (I) inhibit both the lipoxygenase and cyclo-oxygenase pathways of arachidonic acid metabolism in vitro and are useful as anti-inflammatroy or anti-allergic agents, or as agents in the prevention of tissue rejection and other medical conditions which may be alleviated by the inhibition of these pathways.

Accordingly, the present invention relates to heterocylic compounds of formula (I) and salts thereof:



(I)

wherein,

Ar is a monocylic or bicyclic aromatic radical having from 5 to 10 ring atoms selected from carbon and nitrogen optionally substituted in any position of the ring by one or more substituent(s) provided that Ar is other than unsubstituted phenyl;

either G is X and Z is NRR^1 or G is NR and Z is XR^1 wherein X is O or S; and R, R^1, R^4 and R^5 are each the same or different and are each selected from hydrogen, alkyl, unsubstituted phenyl and Ar as defined above, and R and R' may also be allyl.

Examples of aromatic radicals include substituted-phenyl, naphthyl, quinolyl, benzyl, and pyridyl. Particulary preferred aromatic radicals are phenyl and pyridyl, especially wherein 'pyridyl' is selected from 2-pyridyl and 4-pyridyl.

When in the 1-position of the pyrazoline ring, the aromatic ring is preferably substituted and examples of suitable substituents are halo, alkyl (which may itself be optionally substituted by halo), carboxy, alkoxy, nitro, amino (which may itself be optionally substituted by 1 or 2 alkyl groups), hydroxy and alkylsulphonyl of which the alkyl moiety may itself be optionally substituted by halo. Examples of especially suitable Ar substituents are halo (that is: fluoro, chloro, bromo and iodo) and trifluoromethyl. When Ar is substituted-phenyl, the preferred positions of the ring for any substituent are those selected from the 2-, 3-, 4-, 3,4- and 2,6-positions. For example, Ar may be selected from 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 3-trifluoromethyl-4-fluorophenyl, 3-trifluoromethyl-4-chlorophenyl and 3-trifluoromethyl-4-bromophenyl. When Ar is pyridyl, the preferred position of the ring for any substituent is the 5-position. For example, Ar may be selected from 5-chloro-2-pyridyl, 5-bromo-2-pyridyl and 5-iodo-2-pyridyl.

Preferably, both R and R' are other than allyl.

When any of R, R^1, R^4 and R^5 are Ar or phenyl the aromatic ring is preferably unsubstituted. For example, they may be selected from phenyl, 2-pyridyl and 4-pyridyl. R^4 and R^5 are preferably selected from hydrogen and alkyl. When Z is NRR^1, R and R^1 are preferably selected from hydrogen, alkyl, phenyl, 2-pyridyl and 4-pyridyl; and when G is NR and Z is XR^1, R and R^1 are preferably selected from hydrogen and alkyl. Compounds of formula (I) wherein G is X and Z is NRR^1 such as those wherein R is H and R^1 is phenyl or alkyl such as methyl are especally preferred.

Examples of compounds of formula (I) are:

3-(N^2-phenylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N^2-3-pyridylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N^2-methylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N^2-methylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N^2,S-dimethylisothioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N^2,O-dimethylisoureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N-methylthioureido)-1-(5-bromo-6-methyl-2-pyridyl)-2-pyrazoline;

3-(3-butylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

N,S-dimethyl-N^2-[1-(4-chlorophenyl)-2-pyrazolin-3-yl]isothiourea;

3-(3-methylthioureido)-1-(2-naphthyl)-2-pyrazoline;

3-(3-phenylureido)-1-(3-carboxyphenyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(2-pyridyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(3-quinolyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(2-chlorophenyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(3-t-butylphenyl)-2-pyrazoline;

3-(N^2,S-dimethylisothioureido)-1-(2-chlorophenyl)-2-pyrazoline;

N^1,S-dimethyl-N^2-[1-(2-naphthyl)-2-pyrazolin-3-yl]isothiourea;

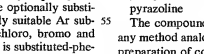
3-(3-isobutylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(3-benzylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline; and

3-(3-allylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline

The compounds of formula (I) may be prepared by any method analogous to those known in the art for the preparation of compounds of analogous structure.

(1) A method for the preparation of compounds of formula (I) wherein G is X and Z is NHR^1 comprises the reaction of an amine of formula (II) with a compound of formula (III)



(II) (III)

wherein one and only one of R^6 and R^7 is

and the other is R^1; and Ar, R^4, R^5, X and R^1 are defined as in formula (I). The reaction may be effected in an inert solvent such as chloroform, preferably with heating.

The compound of formula (II) wherein R^6 is R^1 and the compound of formula (III) wherein R^7 is

may be prepared by reaction of the compound of formula (II) wherein R^6 is

with a compound of formula (IV): CXR^8R^9 (IV) wherein X is as defined in formula (III) and R^8 and R^9 may be the same or different and are each independently selected from halo radicals (e.g. chloro, bromo and iodo).

(2) A method for the preparation of compounds of formula (I) wherein G is NR and Z is XR^1 comprises reaction of the corresponding compound of formula (I) wherein G is X and Z is NHR^1 with an alkyl halide (RR^8 wherein R is as defined in formula (I) and R^8 is as defined in formula (IV), supra).

The compounds of formula (I) may be used in the relief of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, eczema, other inflammatory skin conditions, inflammatory eye conditions including conjunctivitis, pyresis, pain and other conditions associated with inflammation. Such other conditions associated with inflammation include the reduction of tissue necrosis in chronic inflammation, the suppression of tissue rejection following transplant surgery and ulcerative colitis.

The compounds of formula (I) may also be used in the treatment of prophylaxis of allergic conditions and other airway inflammatory conditions such as asthma and of asthma having a non-allergic origin and bronchitis. The compounds may also be useful as antispasmogenic agents.

The amount required of a compound of formula (I) (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula (I) for a mammal suffering from an inflammatory, painful or pyretic condition as defined hereinbefore is 0.5 to 500 mg of base per kilogram bodyweight, the most preferred dosage being 0.5 to 50 mg/kg of mammal bodyweight, for example 5 to 25 mg/kg; administered two or three times daily.

In the case of the treatment of prophylaxis of inflammatory airway conditions, a suitable anti-asthmatic dose of a compound of formula (I) is 1 mg to 10 mg of base per kilogram bodyweight, the most preferred dosage being 10 mg to 5 mg/kg of mammal bodyweight, for example from 1 to 2 mg/kg.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 99.9% by weight of the formulation. Conveniently, unit doses of a formulation contain between 0.1 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 2% by weight of the formulation but the active ingredient may comprise as much as 10% w/w. Formulations suitable for nasal or buccal administration, (such self-propelling powder-dispensing formulations described hereinafter), may comprise 0.1 to 20% w/w, for example about 2% w/w of active ingredient.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical, nasal or buccal administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of

the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented in the form of aqueous eye drops as, for example, a 0.1–1.0% solution.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations such as aerosols and atomizers. The formulations, when dispersed, preferably have a particle size in the range of 10 to 200u.

Such formulations are most preferably in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations, where the active ingredient, as a finely comminuted powder, may comprise up to 99.9% w/w of the formulation. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (i.e. being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder of controlled particle size. Thus the formulation, instead of passing into the lungs, is largely retained in the nasal cavity. These self-propelling formulations may be either powder-dispensing formulations or formulations dispensing the active ingredient as droplets of a solution or suspension.

Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredient, and a liquid propellant having a boiling point if below 65° F. (18° C.) at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more alkyl hydrocarbons or halogenated lower alkyl hydrocarbons or mixtures thereof; chlorinated and fluorinated lower alkyl hydrocarbons are especially preferred. Generally, the propellant constitutes 50 to 99.9% w/w of the formulation whilst the active ingredient constitutes 0.1 to 20% w/w, for example, about 2% w/w, of the formulation.

The pharmaceutically acceptable carrier in such self-propelling formulations may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Surfactants are desirable since they prevent agglomeration of the particles of active ingredient and maintain the active ingredient in suspension. Especially valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. Suitable liquid non-ionic surfactants are those having a hydrophile-lipophile balance (HLB, see Journal of the Society of Cosmetic Chemists Vol. I pp. 311–326 (1949)) of below 10, in particular esters and partial esters of fatty acids with alphatic polyhydric alcohols, for instance, sorbitan monooleate and sorbitan trioleate, known commercially as 'Span 80' (Trade Name) and 'Span 85' (Trade Name), respectively. The liquid non-ionic surfactant may constitute from 0.01 up to 20% w/w of the formulation, though preferably it constitutes below 1% w/w of the formulation. Suitable solid anionic surfactants include alkali metal, ammonium and amine salts of dialkyl sulphosuccinate (where the alkyl groups have 4 to 12 carbon atoms) and alkyl benzene sulphonic acid (where the alkyl group has 8 to 14 carbon atoms). The solid anionic surfactants may constitute from 0.01 up to 20% w/w of the formulation, though preferably below 1% w/w of the composition solid diluents may be advantageously incorporated in such self-propelling formulations where the density of the active ingredient differs substantially from the density of the propellant; also, they help to maintain the active ingredient in suspension. The solid diluent is in the form of a fine powder, preferably having a particle size of the same order as that of the particles of the active ingredient. Suitable solid diluents include sodium chloride, sodium sulphate and sugars.

Formulations of the present invention may also be in the form of a self-propelling formulation wherein the active ingredient is present in solution. Such self-propelling formulations may comprise the active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. The propellant is one or more of these already cited above. Co-solvents are chosen for their solubility in the propellant, their ability to dissolve the active ingredient, and for their having the lowest boiling point consistent with these above-mentioned properties. Suitable co-solvents are lower alkyl alcohols and ethers and mixtures thereof. The co-solvent may constitute 5 to 40% w/w of the formulation, though preferably less than 20% w/w of the formulation. Antioxidant stabilisers may be incorporated in such solution-formulations to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulphites. They are preferably present in an amount of up to 0.25% w/w of the formulation.

Such self-propelling formulations may be prepared by any method known in the art. For example, the active ingredient (either as particles as defined hereinbefore in suspension in a suitable liquid or in up to 20% w/v solution in an acceptable co-solvent, as appropriate) is mixed with any other constituents of a pharamceutically acceptable carrier. The resulting mixture is cooled, introduced into a suitable cooled container and propellant is added thereto in liquid form; and the container is sealed. Alternatively, such self-propelling formulations may be prepared by mixing the active ingredient either in particles as hereinbefore defined or in 2 to 20% w/v alcohol or aqueous solution as appropriate, together with the remaining constituents of the pharmaceutically acceptable carrier other than the propellant; introducing the resulting mixture, optionally with some propellant, into a suitable container; and injecting the propellant, under pressure, into the container at ambient temperature through a valve which comprises a part of the container and is used to control release of the formulation from it. Desirably, the container is purged by removing air from it at a convenient stage in the preparation of the self-propelling formulation.

A suitable container for a self-propelling formulation is one provided with a manually-operable valve and constructed of aluminium, stainless steel or reinforced glass. The valve should, of course, be one having the desired spray characteristics of particle size as hereinbefore defined. Advantageously, the valve is of the type

which delivers a fixed amount of the formulation on the occasion of each operation of the valve, for example, about 50 to 100 microliters of formulation in each delivery.

Formulations of the present invention may also be in the form of an aqueous or dilute alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. Such formulations usually contain a flavouring agent such as saccharin sodium and a volatile oil. A buffering agent such as sodium metabisulphite and a surface active agent may also be included in such a formulation which should also contain a preservative such as methylhydroxybenzoate.

Other formulations suitable for nasal administration include a coarse powder having a particle size of 20 to 500 microns which is administered in the manner if which snuff is taken i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binder, surface active agents, thickeners, lubricants, preservatives eg. methylhydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

Any other therapeutic ingredient may comprise one or more of the following: anti-biotic, anti-fungal and anti-viral agents.

According to the present invention there are therefore provided:

(a) a novel compound of formula (I) or an acid addition salt thereof;

(b) a method for the preparation of the compounds of formula (I);

(c) a pharmaceutical formulation comprising a non-toxic, effective arachidonic acid oxygenation inhibitory amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof a pharmaceutically acceptable carrier therefor;

(d) a method for preparing such formulations;

(e) a method for the prophylaxis or treatment of inflammation in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-inflammatory amount of a compound of formula (I);

(f) a method for the prophylaxis or treatment of pain in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective analgesic amount of a compound of formula (I);

(g) a method for the prophylaxis or treatment of pyresis in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective antipyretic amount of a compound of formula (I);

(h) a method for the prophylaxis or treatment of asthma in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective, antiasthmatic amount of a compound of formula (I);

(i) a method for the inhibition of the lipoxygenase or cyclo-oxygenase pathways of arachidonic acid metabolism comprising the administration of a non-toxic, effective, inhibitory amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof; and

(j) a compound of formula (I) for use in medicine in the inhibition of the lipoxygenase or cyclo-oxygenase pathways of arachidonic acid metabolism

The following Examples are provided by way of an illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius.

EXAMPLE 1

Preparation of 3-(N²-phenylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline

A solution of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (500 mg) and phenylisocyanate (260 mg) in chloroform (10 ml) was heated to reflux for 1 hour. After cooling, the resulting 3-(N²-phenylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline was filtered off and recrystallized from isopropanol, m.p. 230°.

EXAMPLES 2 AND 3

By a method according to that described in Example 1 were prepared the following compounds:

Example 2: 3-(N²-methylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 213°-214°; and

Example 3: 3-(N²-methylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 241°-242°.

EXAMPLE 4

Preparation of 3-(N²-3-pyridylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline

By a method analagous to that described in Example 1, but using n-propanol in place of isopropanol, was prepared 3-(N²-3-pyridylureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline which was isolated as a crystalline solid, m.p. 224°.

Analysis: Required: H, 4.04; N, 20.05; C, 55.02. Found: C, 54.90; H, 4.03; N, 19.88.

EXAMPLE 5

Preparation of 3-(N²,S-dimethylisothioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline

The compound prepared in Example 3 (5 g) and methyliodide (4 ml) in acetone (30 ml) were heated at 65° with stirring. After about 20 minutes all the starting material had dissolved and after a further short time the product started to crystallize out. Heating was continued for 2 hours, then the reaction mixture was cooled in a carbon dioxide bath. The solid product was collected, washed with ethyl acetate and diethyl ether and dried to produce 3-(N²,S-dimethylisothioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline hydriodide monohydrate, m.p. 158°.

Analysis: Required: C, 35.15; H, 3.63; N. 12.61. Found: C, 35.00; H, 3.45; N, 12.64.

EXAMPLE 6

Preparation of 3-(3-methylthioureido)-1-(4-chlorophenyl)-2-pyrazoline

3-Amino-1-(4-chlorophenyl)-2-pyrazoline (1.5 g) (prepared in Reference Example 6 of our European patent specification No. 22-578) and methylisothiocyanate (1.02 g) were heated together at 100° for two hours. The crude product was ground under methanol,

collected by filtration, and recrystallised from acetone to yield 3-(3-methylthioureido)-1-(4-chlorophenyl)-2-pyrazoline, m.p. 237°.

EXAMPLE 7

Preparation of 1-(5-bromo-6-methyl-2-pyridyl)-3-(N-methylthioureido)-2-pyrazoline

3-Amino-1-(5-bromo-6-methyl-2-pyridyl)-2-pyrazoline (4.0 g) and methylisothiocyanate (4.7 g) stirred together at about 120°. A clear melt formed which did not solidify very well and which was kept at 120° for 2 hours. The melt was then treated with S.V.M. (15 ml) and stirred whilst cooling. A clear solid resulted which was collected, washed with S.V.M. and dried in vacuo to yield 3.9 g 1-(5-bromo-6-methyl-2-pyridyl)-3-N-methylthioureido-2-pyrazoline, m.p. 229°–230° (decomp).

EXAMPLE 8

Preparation of 3-(3-Butylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline.

Thiophosgene (11.5 g) was added slowly to a solution of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (23 g) (prepared according to Reference Example 1 of European patent specification No. 22-578) in acetone (250 ml) at 0° in an atmosphere of carbon dioxide. The addition was completed in about 20 minutes and was then allowed to warm to room temperature for 1 hour. The resulting insoluble solid, the hydrochloride of the starting base, was filtered off and washed with fresh acetone. The combined filtrate and washings were evaporated in vacuo to give crude 3-isothiocyanato-1-(3-trifluoromethylphenyl)-2-pyrazoline as a gum (13 g) which subsequently crystallised. This compound was used directly without purification but the presence of the isothiocyanate group was confirmed by infra red spectroscopy which exhibited a broad band in the region of 2005 cm^{-1}. This gum (3.8 g) was suspended in toluene (40 ml) and stirred during the addition of butylamine (1.5 g). When the gum changed into a colourless solid. After 2 hours, the mixture was warmed to about 35° for 10 minutes and then cooled back to room temperature. The resulting solid was collected, washed with a little fresh toluene and recrystallised from propanol in long prisms, m.p. 197°–198° of 3-(3-butylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline.

EXAMPLE 9

N,S-Dimethyl-N^2/(4-chlorophenyl)-2-pyrazolin-3-yl/isothiourea hydriodide

1-(4-Chlorophenyl)-3-(3-methylthioureido)-2-pyrazoline (436 mg) in acetone (50 ml) was treated with methyliodide (0.2 ml) and heated to reflux for two hours. The reaction mixture was cooled to room temperature and the solid produced collected by filtration.

After recrystallisation from n-propanol the N,S-dimethyl-N^2-/1-(4-chlorophenyl)-2-pyrazoline-3-yl/isothiourea hydriodide had m.p. 161°–167°.

EXAMPLE 10

3-(3-Methylthioureido)-1-(2-naphthyl)-2-pyrazoline

3-Amino-1-(2-naphthyl)-2-pyrazoline (1 g) and methylisothiocyanate (1.4 g) were heated at 130° for 7 hours. The cooled reaction mixture was diluted with methanol and the solid product collected by filtration.

After extraction with hot methanol, the insoluble 3-(3-methylthioureido)-1-(2-naphthyl)-2-pyrazoline had m.p. 230°–235° decomp.

EXAMPLE 11

1-(3-Carboxyphenyl)-3-(3-phenylureido)-2-pyrazoline

3-Amino-1-(3-carboxyphenyl)-2-pyrazoline (108 mg) and phenylisocyanate (140 mg) in chloroform (10 ml) were heated to reflux overnight. The resultant solid was collected and dried to yield 1-(3-carboxyphenyl)-3-(3-phenylureido)-2-pyrazoline m.p. 255° decomp.

EXAMPLES 12–15

Following the procedure of Example 6, there were prepared:

Example 12: 3-(3-Methylthioureido)-1-(2-pyridyl)-2-pyrazoline, m.p. 224°.

Example 13: 3-(3-Methylthioureido)-1-(3-quinolyl)-2-pyrazoline, m.p. 227°.

Example 14: 1-(2-Chlorophenyl)-3-(3-methylthioureido)-2-pyrazoline, m.p. 204°–205°.

Example 15: 1-(3-t-Butylphenyl)-3-(3-methylthioureido)-2-pyrazoline.

EXAMPLES 16–17

Following the procedure of Example 9, there were prepared:

Example 16: 1-(2-Chlorophenyl)-3-(N^2,S-dimethylisothioureido)-2-pyrazoline hydriodide, m.p. 139°–140°.

Example 17: N^1,S-Dimethyl-N^2-/1-(2-naphthyl)-2-pyrazolin-3-yl/isothiourea hydriodide, m.p. 155°–156°

EXAMPLES 18–20

Following the procedure of Example 8, there were prepared:

Example 18: 3-(3-Isobutylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 215°–216°.

Example 19: 3-(3-Benzylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 209°.

Example 20: 3-(3-Allylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 223°.

EXAMPLE A: TABLET

	In one tablet
Active Ingredient	5.0 mg
Lactose	82.0 mg
Starch	10.0 mg
Povidone	2.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, lactose and starch. Granulate the powders using a solution of Povidone in purified water. Dry the granule, add the magnesium stearate and compress to produce tablets, 100 mg per tablet.

EXAMPLE B: OINTMENT

Active Ingredient	1.0 mg
White Soft Paraffin	to 100.0 g

Disperse the active ingredient in a small volume of the vehicle. Gradually incorporate this into the bulk to

produce a smooth, homogenous product. Fill into collapsible metal tubes.

EXAMPLE C: CREAM FOR TOPICAL USE

Active Ingredient	1.0 g
Polawax GP 200	20.0 g
Lanolin Anhydrous	2.0 g
White Beeswax	2.5 g
Methyl Hydroxybenzoate	0.1 g
Distilled Water	to 100.00 g

Heat the polawax, beeswax and lanolin together at 60° C. Add a solution of methyl hydroxybenzoate. Homogenise using high speed stirring. Allow the temperature to fall to 50°. Add and disperse the active ingredient. Allow to cool with slow speed stirring.

EXAMPLE D: LOTION FOR TOPICAL USE

Active Ingredient	1.0 g
Sorbitan Monolaurate	0.6 g
Polysorbate 20	0.6 g
Cetostearyl Alcohol	1.2 g
Glycerin	6.0 g
Methyl Hydroxybenzoate	0.2 g
Purified Water B.P.	to 100.00 ml

The methyl hydroxybenzoate and glycerin were dissolved in 70 ml of water at 75° C. The sorbitan monolaurate, Polysorbate 20 and cetostearyl alcohol were melted together at 75° and added to the aqueous solution. The resulting emulsion was homogenised, allowed to cool with continuous stirring and the active ingredient added as a suspension in the remaining water. The whole was stirred until homogenous.

EXAMPLE E: EYE DROPS

Active Ingredient	0.5 g
Methyl Hydroxybenzoate	0.01 g
Propyl Hydroxybenzoate	0.04 g
Purified Water B.P.	to 100.00 ml

The methyl and propyl hydroxybenzoates were dissolved in 70 ml purified water at 75° and the resulting solution then allowed to cool. The active ingredient was added next and the solution made up to 100 ml with purified water. The solution was sterilised by filtration through a membrane filter 0.22 um pore size and packed aseptically into suitable sterile containers.

EXAMPLE F: INJECTION SOLUTION

Active Ingredient	10.0 mg
Water for Injections B.P.	to 1.0 ml

The active ingredient was dissolved in half of the water for injections and then made up to volume and sterilised by filtration. The resulting solution was distributed into ampoules under aseptic conditions.

EXAMPLE G: INHIBITION OF LIPOXYGENASE AND CYCLO-OXYGENASE

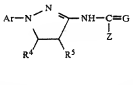
In an enzyme assay according to the method of G. Blackwell and R. J. Flower (Br. J. Pharmac., 63: 36OP (1978)), compounds of the invention were found to have and IC_{50} (uM) for inhibition of each of lipoxygenase and cyclo-oxygenase as indicated in Table I:

TABLE I

Compound	ED_{50} (μM) Cyclo-oxygenase	Lipoxygenase
of Example 1	3	5–10
of Example 2	3	3
of Example 3	1	1
of Example 5	1	1
of Example 6	5	3
of Example 8	10	10
of Example 9	10	10
of Example 10	0.25	1
of Example 13	10	10
of Example 14	10	10
of Example 17	1	1

What is claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Ar is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, benzyl and pyridyl optionally substituted in any position of the ring by one or more substuent(s) selected from fluoro, chloro, bromo, iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, trifluoromethyl, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, lower alkyl, lower alkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl provided that Ar is other than unsubstituted-phenyl;

G is S and Z is NRR^1; and

R, R^1, R^4 and R^5 are each the same or different and are each selected from hydrogen, lower alkyl, and Ar as defined above; and R and R^1 may also be lower alkyl.

2. A compound according to claim 1, wherein

R and R^1 are each the same or different and are each selected from hydrogen, alkyl, unsubstituted-phenyl and Ar as defined in claim 1; and salts thereof.

3. A compound according to claim 2, wherein

Ar is selected from substituted-phenyl, naphthyl, quinolyl, benzyl and pyridyl.

4. A compound according to claim 3 wherein:

R^4 and R^5 are each the same or different and are each selected from hydrogen and lower alkyl.

5. A compound according to claim 4 wherein:

R and R^1 are each the same or different and are each selected from hydrogen, lower alkyl, phenyl, 2-pyridyl and 4-pyridyl.

6. A compound selected from the group consisting of:

3-(N^2-methylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(N-methylthioureido)-1-(5-bromo-6-methyl-2-pyridyl)-2-pyrazoline;

3-(3-butylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(2-naphthyl)-2-pyrazoline;

3-(3-methylthioureido)-1-(2-pyridyl)-2-pyrazoline;
3-(3-methylthioureido)-1-(3-quinolyl)2-pyrazoline;
3-(3-methylthioureido)-1-(2-chlorophenyl)-2-pyrazoline;
3-(3-methylthioureido)-1-(3-t-butylphenyl)-2-pyrazoline;
3-(3-isobutylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline;
3-(3-benzylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline; and
3-(3-allylthioureido)-1-(3-trifluoromethylphenyl)-2-pyrazoline.

7. A pharmaceutical formulation, useful in treating inflammation in mammals, comprising an effective amount of a compound or salt of formula (I), as defined in any of claims 1 to 6, in association with a pharmaceutically acceptable carrier therefor.

8. A formulation according to claim 7 in unit dosage form.

9. A formulation according to claim 7 in the form of capsules, tablets, suppositories, liniments, lotions, creams, ointments, drops or aerosols.

10. A formulation according to claim 7 in a form suitable for ophthalmic administration.

11. A formulation according to claim 10 in the form of aqueous eye drops.

12. A formulation according to claim 7, wherein the compound or salt of formula (I) is further in association with another therapeutic ingredient selected from antibiotic, anti-fungal and anti-viral agents.

13. A method for the prophylaxis or treatment of inflammation in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-inflammatory amount of a compound of formula (I), as defined in any of claims 1 to 6.

14. A method according to claim 13, wherein the amount of the compound of formula (I) is from 0.5 to 50 mg per kilogram of mammal bodyweight.

15. A method for the prophylaxis or treatment of pain in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective analgesic amount of a compound of formula (I), as defined in any of claims 1 to 6.

16. A method according to claim 15, wherein the amount of the compound of formula (I) is from 0.5 to 50 mg per kilogram of mammal bodyweight.

17. A method for the prophylaxis or treatment of pyresis in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-pyretic amount of a compound of formula (I), as defined in any of claims 1 to 6.

18. A method according to claim 17, wherein the amount of the compound of formula (I) is from 0.5 to 50 mg per kilogram of mammal bodyweight.

19. A method for the inhibition of the lipoxygenase or cyclo-oxygenase pathways of arachidonic acid metabolism in a mammal, including man, comprising the administration of an effective inhibitory amount of a compound of formula (I), as defined in any of claims 1 to 6.

20. A method according to claim 19, wherein the amount of the compound of formula (I) is from 0.5 to 50 mg per kilogram of mammal bodyweight.

21. A method of treating the medical symptoms of inflammation in a mammal, which symptoms may be alleviated by the inhibition of arachidonic acid metabolism which comprises administering to said mammal an effective arachidonic acid metabolism inhibiting amount of a compound or salt of claim 1.

* * * * *

Exhibit D

United States Patent [19]

Copp et al.

[11] **Patent Number: 4,572,913**

[45] **Date of Patent: Feb. 25, 1986**

[54] **USE OF 3-(ARYLMETHYLENEAMINO)-1-ARYL-2-PYRAZOLINES IN THE PROPHYLAXIS AND TREATMENT OF INFLAMMATION, PAIN, PYRESIS, AND ASTHMA**

[75] Inventors: **Frederick C. Copp, Beckenham; Albert G. Caldwell, West Wickham; David Collard, Beckenham, all of England**

[73] Assignee: **Burroughs Wellcome Co., Research Triangle Park, N.C.**

[21] Appl. No.: **331,009**

[22] Filed: **Dec. 15, 1981**

[30] **Foreign Application Priority Data**

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Mar. 18, 1981 [GB] United Kingdom 8108478

[51] **Int. Cl.**[4] **A61K 31/415**; A61K 31/44; A61K 31/47; C07D 231/06

[52] **U.S. Cl.** **514/403**; 514/313; 514/314; 514/333; 514/341; 548/379

[58] **Field of Search** ..... 542/414, 422, 424; 424/258, 263, 266, 273 P; 514/313, 314, 333, 341, 407; 548/379

[56] **References Cited**

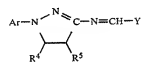
PUBLICATIONS

Duffin et al., J. Chem. Soc. 1954, pp. 408–415.
Kost et al., Fhur. Obshchei Khim. 29, pp. 498–502 (1959), [Translation and Abstract].

Primary Examiner—Richard A. Schwartz
Assistant Examiner—Kurt G. Briscoe
Attorney, Agent, or Firm—Donald Brown

[57] **ABSTRACT**

Compounds of formula (I)



(I)

inhibit both the cyclo-oxygenase and lipoxygenase pathways of arachidonic acid oxygenation and are useful in medicine as, e.g., anti-inflammatory and anti-asthmatic agents.

The compounds may be administered as the raw chemical or in association with a carrier as a pharmaceutical formulation.

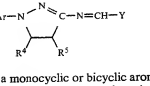
The compounds may be prepared by methods analogous to those known in the art, e.g., by the method of Duffin and Kendall in J. Chem. Soc. (1954), 408–415, or by other methods.

17 Claims, No Drawings

USE OF 3-(ARYLMETHYLENEAMINO)-1-ARYL-2-PYRAZOLINES IN THE PROPHYLAXIS AND TREATMENT OF INFLAMMATION, PAIN, PYRESIS, AND ASTHMA

This invention relates to heterocyclic compounds and their preparation and to the use of such compounds of pharmaceutical formulations thereof in medicine in a mammal, including man, as e.g. anti-inflammatory or anti-allergic agents or as agents in the prevention of tissue rejection.

Accordingly, the present invention relates to heterocyclic compounds of formula (I) and salts thereof:



(I)

wherein, Y is a monocyclic or bicyclic aromatic radical having from 5 to 10 ring atoms selected from carbon and nitrogen optionally substituted in any position of the ring by one or more substituent(s); R^4 and R^5 are each the same or different and are each selected from hydrogen, alkyl or Y as defined above; Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

Examples of Ar include substituted-phenyl, naphthyl, quinolyl and pyridyl. Particularly preferred aromatic radicals are substituted-phenyl and pyridyl, especially wherein 'pyridyl' is selected from 2-pyridyl and 4-pyridyl.

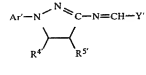
The aromatic ring is preferably substituted and examples of suitable substituents are halo, alkyl (which may itself be optionally substituted by halo), carboxy, alkoxy, nitro, amino (which may itself be optionally substituted by 1 or 2 alkyl groups), hydroxy and alkyl-sulphonyl of which the alkyl moiety may itself be optionally substituted by halo. Examples of especially suitable Ar substituents are halo (that is: fluoro, chloro, bromo and iodo) and trifluoromethyl. When Ar is substituted-phenyl, the preferred positions of the ring for the substituent(s) are those selected from the 2-, 3-, 4-, 3,4- and 2,6-positions. For example, Ar may be selected from 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 3-trifluoromethyl-4-fluorophenyl, 3-trifluoromethyl-4-chlorophenyl and 3-trifluoromethyl-4-bromophenyl. When Ar is pyridyl, the preferred position of the ring for any substituent is the 5-position. For example, Ar may be selected from 5-chloro-2-pyridyl,5-bromo-2-pyridyl and 5-iodo-2-pyridyl.

When any of R^4 and R^5 are Y the aromatic ring is preferably unsubstituted. For example, R^4 and R^5 may be selected from phenyl, 2-pyridyl and 4-pyridyl, but are preferably selected from hydrogen and alkyl.

Y is preferably a monocyclic aromatic radical having either from 3 to 7 ring atoms selected from carbon and nitrogen or a monocyclic or bicyclic aromatic radical of from 5 to 10 carbon atoms. Examples of such aromatic radicals are phenyl, pyridyl, naphthyl and pyrrolyl. When Y is substituted in the aromatic ring, the substituents may be selected from those examples described hereinbefore in the definition of 'Ar'. The preferred positions of the ring for any substituent are those selected from the 2-, 2,4- and 2,6-positions. For example,

Y may be selected from 2-hydroxyphenyl and 2,4-dihydroxyphenyl.

A subclass of the compounds of formula (I) are compounds of formula (IA)



(IA)

wherein

Y' is phenyl, pyridyl, pyrrolyl, naphthyl or quinolyl, each of which may optionally be substituted by one or more of halo, alkyl, alkoxy and hydroxy groups;

R^4 and R^5 are the same or different and are selected from hydrogen and alkyl; and

Ar' is pyridyl, quinolyl or substituted-phenyl, each of which pyridyl and quinolyl may be optionally substituted by one or more substituents, and the substituents are selected from halo, alkyl (which may itself be optionally substituted by halo), alkoxy and carboxyl groups.

Examples of compounds of formula (I) are:

3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-benzylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(2,4-dihydroxybenzylideneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(2-pyridylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(2-pyrrolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-salicylideneamino-1-(2-pyridyl)-2-pyrazoline;

3-(3-quinolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline;

3-salicylideneamino-1-(3-quinolyl)-2-pyrazoline;

3-(4-chlorobenzylideneamino)-1-(4-chlorophenyl)-2-pyrazoline;

1-(4-bromo-3-trifluoromethylphenyl)-3-(2-hydroxybenzylideneamino)-2-pyrazoline;

1-(4-bromo-3-trifluoromethylphenyl)-3-(4-methoxybenzylideneamino)-2-pyrazoline;

3-benzylideneamino-1-(3-t-butylphenyl)-2-pyrazoline;

3-benzylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

1-(5-bromo-6-methyl-2-pyridyl)-3-salicylideneamino-2-pyrazoline;

1-(5-bromo-6-methyl-2-pyridyl)-3-(1-naphthylmethyleneamino)-2-pyrazoline;

4-methyl-3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-benzylideneamino-1-(4-methoxyphenyl)-2-pyrazoline;

3-benzylideneamino-1-(3-carboxylphenyl)-2-pyrazoline;

3-(2-hydroxy-1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

1-(2-chlorophenyl)-3-(2-hydroxy-1-naphthylmethyleneamino)-2-pyrazoline.

The compounds of formula (I) may be prepared by any method known in the art for the preparation of compounds of analogous structure, for example, by the

method of G. F. Duffin and J. D. Kendall in J. Chem. Soc. (1954), 408–415.

The compounds of formula (I) may be used in the relief of rheumatoid arthritis, rheumatoid spondylitis, osteroarthritis, gouty arthritis and other arthritic conditions; inflamed joints; eczema, other inflammatory skin conditions; inflammatory eye conditions including conjunctivitis; pyresis and other conditions associated with inflammation and pain. Such other conditions associated with inflammation include the reduction of tissue necrosis in chronic inflammation, the suppression of tissue rejection following transplant surgery and ulcerative colitis.

The compounds of formula (I) may also be used in the treatment or prophylaxis of allergic conditions and other airway inflammatory conditions such as asthma and of asthma having a non-allergic origin and bronchitis. The compounds may also be useful as antispasmogenic agents.

The amount required of a compound of formula (I) (herinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula (I) for a mammal suffering from an inflammatory, painful or pyretic condition as defined hereinbefore is 0.5 to 500 mg of base per kilogram bodyweight, the most preferred dosage being 0.5 to 50 mg/kg of mammal bodyweight, for example 5 to 25 mg/kg; administered two or three times daily.

In the case of the treatment or prophylaxis of inflammatory airway conditions, a suitable anti-asthmatic dose of a compound of formula (I) is 1 mg to 10 mg of base per kilogram bodyweight, the most preferred dosage being 1 mg to 5 mg/kg of mammal bodyweight, for example from 1 to 2 mg/kg.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 99.9% by weight of the formulation. Conveniently, unit doses of a formulation contain between 0.1 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 2% by weight of the formulation but the active ingredient may comprise as much as 10% w/w. Formulations suitable for nasal or buccal administration, (such self-propelling powder-dispensing formulations described hereinafter), may comprise 0.1 to 20% w/w, for example about 2% w/w of active ingredient.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical, nasal or buccal administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, applications; oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented in the form of aqueous eye drops as, for example, a 0.1–1.0% solution.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations such as aerosols and atomizers. The formulations, when dispersed, preferably have a particle size in the range of 10 to 200u.

Such formulations are most preferably in the form of a finely comminuted powder for pulmonary administration from a powder inhalation device or self-propelling pwder-dispensing formulations, where the active ingredient, as a finely comminuted powder, may comprise up to 99.9% w/w of the formulation. In the case of self-propelling solution and spray formulations, the effect may be achieved either by choice of a valve having the desired spray characteristics (i.e. being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder if controlled particle size. Thus the formulation, instead of passing into the lungs, is largely retained in the nasal cavity. These self-propelling formulations may be either powder-dispensing formulations or formula-

tions dispensing the active ingredient as droplets of a solution or suspension.

Self-propelling powder-dispensing formulations preferably comprise dispersed particles of solid active ingredient, and a liquid propellant having a boiling point if below 65° F. (18° C.) at atmospheric pressure. The liquid propellant may be any propellant known to be suitable for medicinal administration and may comprise one or more lower alkyl hydrocarbons or halogenated lower alkyl hydrocarbons or mixtures thereof; chlorinated and fluorinated lower alkyl hydrocarbons are especially preferred. Generally, the propellant constitutes 50 to 99.9% w/w of the formulation whilst the active ingredient constitutes 0.1 to 20% w/w, for example, about 2% w/w, of the formulation.

The pharmaceutically acceptable carrier in such self-propelling formulations may include other constituents in addition to the propellant, in particular a surfactant or a solid diluent or both. Surfactants are desirable since they prevent agglomeration of the particles of active ingredient and maintain the active ingredient in suspension. Especially valuable are liquid non-ionic surfactants and solid anionic surfactants or mixtures thereof. Suitable liquid non-ionic surfactants are those having a hydrophile-lipophile balance (HLB, see Journal of the Society of Cosmetic Chemists Vol. 1 pp. 311-326 (1949)) of below 10, in particular esters and partial esters of fatty acids with aliphatic polyhydric alcohols, for instance, sorbitan monooleate and sorbitan trioleate, known commercially as 'Span 80' (Trade Name) and 'Span 85' (Trade Name), respectively. The liquid non-ionic surfactant may constitute from 0.01 up to 20% w/w of the formulation, though preferably it constitutes below 1% w/w of the formulation. Suitable solid anionic surfactants include alkali metal, ammonium and amine salts of dialkyl sulphosuccinate (where the alkyl groups have 4 to 12 carbon atoms) and alkyl benzene sulphonic acid (where the alkyl group has 8 to 14 carbon atoms). The solid anionic surfactants may constitute from 0.01 up to 20% w/w of the formulation, though preferably below 1% w/w of the composition solid diluents may be advantageously incorporated in such self-propelling formulations where the density of the active ingredient differs substantially from the density of the propellant; also, they help to maintain the active ingredient in suspension. The solid diluent is in the form of a fine powder, preferably having a particle size of the same order as that of the particles of the active ingredient. Suitable solid diluents include sodium chloride, sodium sulphate and sugars.

Formulations of the present invention may also be in the form of a self-propelling formulation wherein the active ingredient is present in solution. Such self-propelling formulations may comprise the active ingredient, propellant and co-solvent, and advantageously an antioxidant stabiliser. The propellant is one or more of these already cited above. Co-solvents are chosen for their solubility in the propellant, their ability to dissolve the active ingredient, and for their having the lowest boiling point consistent with these above-mentioned properties. Suitable co-solvents are lower alkyl alcohols and mixtures thereof. The co-solvent may constitute 5 to 40% w/w of the formulation, though preferably less than 20% w/w of the formulation. Antioxidant stabilisers may be incorporated in such solution-formulations to inhibit deterioration of the active ingredient and are conveniently alkali metal ascorbates or bisulphites. They are preferably present in an amount of up to 0.25% w/w of the formulation.

Such self-propelling formulations may be prepared by any method known in the art. For example, the active ingredient (either as particles as defined hereinbefore in suspension in a suitable liquid or in up to 20% w/w solution in an acceptable co-solvent, as appropriate) is mixed with any other constituents of a pharmaceutically acceptable carrier. The resulting mixture is cooled, introduced into a suitable cooled container and propellant is added thereto in liquid form; and the container is sealed. Alternatively, such self-propelling formulations may be prepared by mixing the active ingredient either in particles as hereinbefore defined or in 2 to 20% w/v alcohol or aqueous solution as appropriate, together with the remaining constituents of the pharmaceutically acceptable carrier other than the propellant; introducing the resulting mixture, optionally with some propellant, into a suitable container; and injecting the propellant, under pressure, into the container at ambient temperature through a valve which comprises a part of the container and is used to control release of the formulation from it. Desirably, the container is purged by removing air from it at a convenient stage in the preparation of the self-propelling formulation.

A suitable container for a self-propelling formulation is one provided with a manually-operable valve and constructed of aluminium, stainless steel or reinforced glass. The valve should, of course, be one having the desired spray characteristics of particle size as hereinbefore defined. Advantageously, the valve is of the type which delivers a fixed amount of the formulation on the occasion of each operation of the valve, for example, about 50 to 100 microliters of formulation in each delivery.

Formulations of the present invention may also be in the form of an aqueous or dilute alcoholic solution, optionally a sterile solution, of the active ingredient for use in a nebuliser or atomiser, wherein an accelerated air stream is used to produce a fine mist consisting of small droplets of the solution. Such formulations usually contain a flavouring agent such as saccharin sodium and a volatile oil. A buffering agent such as sodium metabisulphite and a surface active agent may also be included in such a formulation which should also contain a preservative such as methylhydroxybenzoate.

Other formulations suitable for nasal administration include a coarse powder having a particle size of 20 to 500 microns which is administered in the manner if which snuff is taken i.e. by rapid inhalation through the nasal pasage from a container of the powder held close up to the nose.

In addition to the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binder, surface active agents, thickeners, lubricants, preservatives eg. methylhydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

Any other therapeutic ingredient may comprise one or more of the following: anti-biotic, anti-fungal and anti-viral agents.

According to the present invention there are therefore provided:

(a) a novel compound of formula (I) or an acid addition salt thereof;

(b) a method for preparing a compound of formula (I);

(c) a pharmaceutical formulation comprising a non-toxic, effective arachidonic acid oxygenation inhibitory amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor;

(d) a method for preparing such formulations;

(e) a method for the prophylaxis or treatment of inflammation in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-inflammatory amount of a compound of formula (I);

(f) a method for the prophylaxis or treatment of pain in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective analgesic amount of a compound of formula (I);

(g) a method for the prophylaxis or treatment of pyresis in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-pyretic amount of a compound for formula (I);

(h) a method for the prophylaxis or treatment of asthma in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective, anti-asthmatic amount of a compound of formula (I);

(i) a method for the inhibition of a pathway of arachidonic acid oxygenation selected from the lipoxygenase and cyclo-oxygenase pathways, comprising the administration of a non-toxic, effective, inhibitory amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof; and

(j) a compound of formula (I) for use in medicine in the inhibition of the lipoxygenase or cyclo-oxygenase pathways of arachidonic acid metabolism.

The following examples are provided by way of an illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius.

EXAMPLE 1

Preparation of 3-(2,4'-carboxybutoxy-6-hydroxybenzylidine-amino)-1-(3-trifluoromethylphenyl)-2-pyrazoline

3-Amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (438 mg) in methanol (4 ml) was mixed together with 2-4'-carboxybutoxy-6-hydroxybenzaldehyde (476 mg). A deep orange rapidly developed. The mixture was heated to reflux for 1½ hours during which time the reaction mixture set to a semi-solid mass. The mixture was cooled to 0° and the solid filtered off, washed with fresh methanol and dried in vacuo to produce 3-(2-4'-carboxybutoxy-6-hydroxybenzylideneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 179.1°.

Analysis: Required: C, 58.79; H, 4.93; N, 9.35; Found: C, 58.98; H, 5.00; N, 9.19.

EXAMPLE 2

Preparation of 3-(2-pyridylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline

3-Amino-1-(3-trifluoromethylphenyl)-2-pyrazoline in methanol (23 ml) was stirred together with 2-pyridylaldehyde at room temperature for 2 hours and then under reflux for a further 2 hours. Thin layer chromatography (SiO_2, ethyl acetate) indicated that the reaction was substantially complete. After standing overnight, additional 2-pyridylaldehyde (0.5 g) was added and heating was continued for 2 hours. TLC again indicated that no further reaction had occurred. The reaction mixture was evaporated in vacuo to yield an orange-coloured solid which was stirred for 45 minutes in aqueous ethanol (3:1) and 3-(2-pyridylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline was collected, m.p. 155.6°.

Analysis: $C_{16}H_{13}F_3N_4$; Required: C, 60.38; H, 4.11; N, 17.60; Found: C, 60.29; H, 4.18; N, 17.58.

EXAMPLE 3

Preparation of 3-(2-pyrrolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline

3-Amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (0.6 g) in n-butanol (4 ml) was heated together with 2-pyrrolylaldehyde (0.25 g) to 100° overnight under a nitrogen atmosphere. TLC (see example 1) indicated that a partial reaction had occurred. Heating was continued for a further 24 hours after which time little further reaction had occurred. The reaction mixture was left at room temperature under a nitrogen atmosphere for 4 days during which time dark-coloured crystals had formed which were collected and re-crystallized from aqueous isopropanol. The product was 3-(2-pyrrolylmethyleneamino)-1-(3-trilfuoromethylphenyl)-2-pyrazoline, m.p. 144°-145°.

Analysis: $C_{15}H_{13}F_3N_4$; Required: C, 58.82; H, 4.28; N, 18.29; Found: C, 59.04; H, 4.20; N, 18.5.

EXAMPLE 4

Preparation of 3-salicylidenamino-1-(3-trifluoromethylphenyl)-2-pyrazoline

A. A solution of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (2.29 g) and salicylaldehyde (1.2 g) in methanol (22.9 ml) was heated to reflux for 30 minutes. The resulting semi-solid mass was cooled and then filtered to give an orange-coloured solid which was re-crystallized from ethanol to produce 3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline m.p. 159.1° (yield 1.7 g).

Analysis: $C_{17}H_{14}F_3N_3O$; Required: C, 61.3; H, 4.1; N, 12.6; Found: C, 61.06; H, 4.36; N, 12.11.

B. Salicylaldehyde (80 mg) was added to a solution of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline hydrochloride (130 mg) in water (5 ml). The salicylaldehyde layer rapidly turned orange and after about 10 minutes a semi-solid mass had formed. Ethanol (1 ml) was added to give a clear solid. The mixture was kept overnight at room temperature and the product was collected and washed with water containing 5% ethanol and finally, dried in vacuo to produce 3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 155.8° (yield 130 mg). The product was then re-crystallized with ethanol and on subsequent analysis, was found to be identical with that described in paragraph A.

EXAMPLE 5

Preparation of 3-salicylideneamino-1-(2-pyridyl)-2-pyrazoline

3-Amino-1-(2-pyridyl)-2-pyrazoline (1.6 g) and salicylaldehyde (1.2 g) were dissolved together with methanol (16 ml). The resulting solution was heated to reflux and after about 15 minutes a crystalline solid separated. After another 15 minutes at reflux the suspension was cooled and the separated 3-salicylideneamino-1-(2-pyridyl)-2-pyrazoline was re-

crystallized from methanol m.p. 242°–243° (yield 500 mg).

Analysis: $C_{15}H_{14}N_4O$; Required: C, 67.65; H, 5.3; N, 21.04; Found: C, 67.60; H, 5.34; N, 21.38.

EXAMPLE 6

Preparation of 3-(3-quinolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline

A mixture of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (prepared in Reference Example 1 of our European patent specification No. 22-578) (0.73 g), 3-quinoline carboxaldehyde (0.5 g) and 1 drop glacial acetic acid in methanol (10 ml) was heated to reflux for thirty minutes. After cooling, the solid product was collected and recrystallized from ethanol, and subsequently from ethyl acetate and from toluene to afford 3-(3-quinolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 209°–210°.

EXAMPLE 7

Preparation of 3-(1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline

A solution of 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline (prepared in Reference Example 1 of our European patent specification No. 22-578) (10 g) and 1-naphthaldehyde (6.81 g) containing four drops of glacial acetic acid was heated to reflux in ethanol (50 ml) for twenty four hours. The resultant solid was collected and recrystallized from propan-1-ol to yield 3-(1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p.173°.

EXAMPLE 8

Preparation of 3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline

Example 8A: 3-amino-1-(2-naphthyl)-2-pyrazoline

2-Hydrazinonaphthalene (5 g) was added to a solution of sodium (0.7 g) in dried S.V.M. (20 ml) in a nitrogen atmosphere at 0°–5°. Acrylonitrile (1.8 g) was then added slowly and the resulting mixture allowed to attain room temperature over about 1 hour.

The mixture was then heated to reflux; after about 30 minutes it deposited a crystalline solid and after about 45 minutes a semi-solid mass had formed. After a total heating time of 1 hour, the mixture was allowed to cool and the solid filtered off with care.

The filtrate was deep purple but the residue was a clear yellow solid which was ground up with water, filtered and re-ground with S.V.M. After further filtering and grinding with S.V.M., the product was finally filtered, washed with S.V.M. and dried in vacuo to yield 4.4 g of 3-amino-1-(2-naphthyl)-2-pyrazoline, m.p. 190°–191°.

Example 8B: 3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline

The amino compound prepared in Example 8A (500 mg) was suspended in S.V.M. (25 ml) together with 4-methylbenzaldehyde (300 mg) and 1 drop of glacial acetic acid. The mixture was stirred at reflux temperature for 2 hours. A dark orange solid formed and the reaction mixture was cooled and filtered to produce a dark yellow solid.

The product was washed with methanol and dried in vacuo to give 3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline, m.p. 184°–186°.

EXAMPLE 9

Preparation of 3-salicylideneamino-1-(3-quinolyl)-2-pyrazoline

3-Amino-1-(3-quinolyl)-2-pyrazoline (prepared in Example 10 of our co-pending application No. (A.629)) (1.06 g, 0.005 mol) was added to a solution of salicylaldehyde (0.61 g, 0.005 mol) in methanol (8 ml). The mixture was refluxed for ½ hour and then the solid filtered off.

The solid was refluxed in methanol (200 ml) for ½ hour, the insoluble material filtered off and the product recrystallized from 2-ethoxyethanol with charcoaling to yield 0.14 g 3-salicylideneamino-1-(3-quinolyl)-2-pyrazoline, m.p. 288°–289°.

EXAMPLE 10

Preparation of 3-(4-chlorobenzylideneamino)-1-(4-chlorophenyl)-2-pyrazoline

3-Amino-1-(4-chlorophenyl)-2-pyrazoline (prepared in Reference Example 6 of our European patent specification No. 22-578) (1.95 g) in S.V.M. (5 ml) was mixed with excess 4-chlorobenzaldehyde (1.50 g) and the mixture was heated to reflux after the addition of 1 drop of glacial acetic acid. A virtually clear solution formed which rapidly crystallised to form a bright orange product which was collected, washed with S.V.M. and dried in vacuo to produce 2.95 g 3-(4-chlorobenzylideneamino)-1-(4-chlorophenyl)-2-pyrazoline, m.p. 193°–195° (decomp).

EXAMPLE 11

Preparation of 1-(4-bromo-3-trifluoromethylphenyl)-3-(2-hydroxybenzylideneamino)-2-pyrazoline

3-Amino-1-(4-bromo-3-trifluoromethylphenyl)-2-pyrazoline (prepared in Example 39 of our European patent specification No. 22-578) (140 mg) and salicylaldehyde (100 mg) were dissolved together in methanol (2 ml) and 1 drop of glacial acetic acid. The mixture was heated to reflux for 1 hour. During this time a deep orange-red colour developed and the mixture crystallised. It was kept at 0° for 3 hours, then the solid was collected, washed with methanol and dried in vacuo to yield 150 mg 1-(4-bromo-3-trifluoromethylphenyl)-3-(2-hydroxybenzylideneamino)-2-pyrazoline, m.p. 170° (decomp).

EXAMPLE 12

Preparation of 1-(4-bromo-3-trifluoromethylphenyl)-3-(4-methoxybenzylideneamino)-2-pyrazoline

3-Amino-1-(4-bromo-3-trifluoromethylphenyl)-2-pyrazoline (prepared in Example 39 of our European patent specification No. 22-578) (240 mg) in S.V.M. (5 ml) together with 4-methoxybenzaldehyde (160 mg) and 1 drop of glacial acetic acid were heated to reflux for 1 hour. A yellow product separated which was collected, washed with methanol and dried in vacuo to yield 300 mg 1-(4-bromo-3-trifluoromethylphenyl)-3-(4-

methoxybenzylideneamino)-2-pyrazoline, m.p. 175°-176° (decomp).

EXAMPLE 13

3-Amino-1-(3-t-butylphenyl)-2-pyrazoline

3-t-Butylaniline hydrochloride (5 g) in concentrated hydrochloric acid (8 ml) was stirred at 0° whilst a solution of sodium nitrite (1.86 g) in water (2.4 ml) was slowly added. The mixture was kept at 0° for 1 hour and, after filtering (at 0°), it was treated dropwise with a solution of stannous chloride dihydrate (18.2 g) in concentrated hydrochloric acid (18.8 ml). A pink-coloured solid separated. After 1 hour, this solid was filtered off and washed with saturated aqueous sodium chloride. The resulting salt was converted into base in the usual way to give 3-t-butylphenylhydrazine, b.p. 88°-90°/0.25 mm Hg.

This hydrazine (1.2 g) was then added to a solution of sodium (0.029 g) in ethanol (1.5 ml) at room temperature in an atmosphere of nitrogen. The resulting solution was cooled to −10°, acrylonitrile (0.24 ml) added and the mixture heated to reflux for 5 hours. The solid which separated on cooling was recrystallized from light petroleum (b.p. 80°-100°) to give 3-amino-1-(t-butylphenyl)-2-pyrazoline, m.p. 113.5° (yield 648 mg).

EXAMPLE 14

3-benzylideneamino-1-(3-t-butylphenyl)-2-pyrazoline

3-Amino-1-(3-t-butylphenyl)-2-pyrazoline (500 mg) was reacted with benzaldehyde (500 mg) in boiling methanol (5 ml) in the presence of glacial acetic acid (1 drop). After some 4 hours, the mixture was cooled and 3-benzylideneamino-1-(3-t-butylphenyl)-2-pyrazoline separated in crystals m.p. 140°-141°, (yield 500 mg).

EXAMPLES 15 to 22

By a method analogous to that described in detail in the foregoing Examples were also prepared the following:

EXAMPLE 15

3-Benzylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 162°-163°.

EXAMPLE 16

1-(5-Bromo-6-methyl-2-pyridyl)-3-salicylideneamino-2-pyrazoline, m.p. 215°-216°.

EXAMPLE 17

1-(5-Bromo-6-methyl-2-pyridyl)-3-(1-naphthylmethyleneamino)-2-pyrazoline, m.p. 199°.

EXAMPLE 18

4-Methyl-3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 105°-106°.

EXAMPLE 19

3-Benzylideneamino-1-(4-methoxyphenyl)-2-pyrazoline, m.p. 199°-200°.

EXAMPLE 20

3-Benzylideneamino-1-(3-carboxylphenyl)-2-pyrazoline

3-Amino-1-(3-carboxyphenyl)-2-pyrazoline (850 mg) in methanol (10 ml) was treated with benzaldehyde (870 mg) and glacial acetic acid (1 drop). The mixture was heated to reflux for 7 hours, then left to cool overnight. The resultant product was filtered off and recrystallised from n-propanol to yield 3-benzylideneamino-1-(3-carboxyphenyl)-2-pyrazoline, m.p. 185°.

EXAMPLE 21

3-(2-Hydroxy-1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline, m.p. 247°-249°.

EXAMPLE 22

1-(2-Chlorophenyl)-3-(2-hydroxy-1-naphthylmethyleneamino)-2-pyrazoline, m.p. 195°-197°.

EXAMPLE A

Tablet

In one tablet	
Active Ingredient	5.0 mg
Lactose	82.0 mg
Starch	10.0 mg
Povidone	2.0 mg
Magnesium stearate	1.0 mg

Mix together the active ingredient, lactose and starch. Granulate the powders using a solution of povidone in purified water. Dry the granules, add the magnesium stearate and compress to produce tablets, 100 mg per tablet.

EXAMPLE B

Ointment

Active Ingredient	1.0 g
White soft paraffin to	100.0 g

Disperse the active ingredient in a small volume of the vehicle. Gradually incorporate this into the bulk to produce a smooth, homogeneous product. Fill into collapsible metal tubes.

EXAMPLE C

Cream for Topical Use

Active Ingredient	1.0 g
Polawax GP 200	20.0 g
Lanolin Anhydrous	2.0 g
White Beeswax	2.5 g
Methyl Hydroxybenzoate	0.1 g
Distilled Water to	100.0 g

Heat the polawax, beeswax and lanolin together at 60°. Add a solution of methyl hydroxybenzoate. Homogenise using high speed stirring. Allow the temperature to fall to 50°. Add and disperse the active ingredient. Allow to cool with slow speed stirring.

EXAMPLE D

Lotion for Topical Use

Active Ingredient	1.0 g
Sorbitan Monolaurate	0.6 g
Polysorbate 20	0.6 g
Cetostearyl Alcohol	1.2 g
Glycerin	6.0 g
Methyl Hydroxybenzoate	0.2 g
Purified Water to	100.0 ml

The methyl hydroxybenzoate and glycerin were dissolved in 70 ml of the water at 75° C. The sorbitan monolaurate, polysorbate 20 and cetostearyl alcohol were melted together at 75° and added to the aqueous solution. The resulting emulsion was homogenised, allowed to cool with continuous stirring and the active ingredient added as a suspension in the remaining water. The whole was stirred until homogenous.

EXAMPLE E

Eye Drops

Active Ingredient	0.5 g
Methyl Hydroxybenzoate	0.01 g
Propyl Hydroxybenzoate	0.04 g
Purified Water B.P. to	100.00 ml

The methyl and propyl hydroxybenzoates were dissolved in 70 ml purified water at 75° and the resulting solution then allowed to cool. The active ingredient was added next and the solution made up to 100 ml with purified water. The solution was sterilised by filtration through a membrane filter 0.22 um pore size and packed aseptically into suitable sterile containers.

EXAMPLE F

Injection Solution

Active Ingredient	10.0 mg
Water for Injections B.P.	1.0 ml

The active ingredient was dissolved in half of the Water for Injections and then made up to volume and sterilised by filtration. The resulting solution was distributed into ampoules under asceptic conditions.

EXAMPLE G

Inhibition of Lipoxygenase and Cyclo-oxygenase

In an enzyme assay according to the method of G. Blackwell and R. J. Flower (Br.J.Pharmac., 63: 36O(1978)), compounds of the invention were found to have an IC_{50} (uM) for inhibition of each of lipoxygenase and cyclo-oxygenase as indicated in Table I:

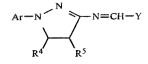
TABLE I

Compound	IC_{50} (μM) Cyclo-oxygenase	Lipoxygenase
of Example 1	<3	10-20
of Example 2	1	~3
of Example 3	<1	1
of Example 4	~3	~3
of Example 7	10	6
of Example 8	5	12
of Example 11	~5	>10
of Example 12	~1	~1
of Example 13	<1	<1
of Example 15	~3	<1
of Example 18	~1	~1

What we claim is:

1. 3-Salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline.

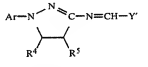
2. A pharmaceutical formulation useful in treating inflammation in mammals comprising an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, mono-alkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R^4 and R^5 are each the same or different and are each selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

3. A formulation according to claim 2 in which the compound or a pharmaceutically acceptable salt thereof is of formula (IA):



(IA)

wherein, Y is phenyl, pyridyl, naphthyl or quinolyl, each of which may optionally be substituted by one or more of halo, alkyl, alkoxy and hydroxy groups; R^4 and R^5 are the same or different and are each selected from hydrogen and alkyl; and Ar is pyridyl, quinolyl or substituted-phenyl, each of which pyridyl and quinolyl may be optionally substituted by one or more substituents, and the substituents are selected from halo, alkyl (which may itself be optionally substituted by halo), alkoxy and carboxyl groups.

4. A pharmaceutical formulation useful in treating inflammation in humans comprising an effective amount of a compound selected from:

3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-benzylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(2,4-dihydroxybenzylideneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(2-pyridylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-salicylideneamino-1-(2-pyridyl)-2-pyrazoline;

3-(3-quinolylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;

3-(1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)2-pyrazoline;

3-(4-methylbenzylideneamino)-1-(2-naphthyl)-2-pyrazoline;

3-salicylideneamino-1-(3-quinolyl)-2-pyrazoline;

3-(4-chlorobenzylideneamino)-1-(4-chlorophenyl)-2-pyrazoline;

3-(2-hydroxybenzylideneamino)-1-(4-bromo-3-trifluoromethylphenyl)-2-pyrazoline;

3-(4-methoxybenzylideneamino)-1-(4-bromo-3-trifluoromethylphenyl)-2-pyrazoline;

3-benzylideneamino-1-(3-t-butylphenyl)-2-pyrazoline;

3-salicylideneamino-1-(5-bromo-6-methyl-2-pyridyl)-2-pyrazoline;
3-(1-naphthylmethyleneamino)-1-(5-bromo-6-methyl-2-pyridyl)-2-pyrazoline;
4-methyl-3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline;
3-benzylideneamino-1-(4-methoxyphenyl)-2-pyrazoline;
3-benzylideneamino-1-(3-carboxyphenyl)-2-pyrazoline;
3-(2-hydroxy-1-naphthylmethyleneamino)-1-(3-trifluoromethylphenyl)-2-pyrazoline;
3-(2-hydroxy-1-naphthylmethyleneamino)-1-(2-chlorophenyl)-2-pyrazoline or a pharmaceutically acceptable salt thereof.

5. A formulation according to claim **2** in unit dosage form.

6. A formulation according to claim **2** in the form of capsules, tablets, suppositories, liniments, lotions, creams ointments, drops or aerosols.

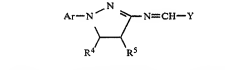
7. A formulation according to claim **2** in a form suitable for ophthalmic administration.

8. A formulation according to claim **2** in the form of aqueous eye drops.

9. A formulation according to claim **2**, wherein the compound or salt of formula (I) is further in association with another therapeutic ingredient selected from antibiotic, anti-fungal and anti-viral agents.

10. A pharmaceutical formulation useful in treating inflammation in mammals comprising an effective amount of 3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline or a pharmaceutically acceptable salt thereof.

11. A method for prophylaxis or treatment of inflammation in a mammal in need thereof, including man, comprising the administration to said mammal of a non-toxic, effective anti-inflammatory amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



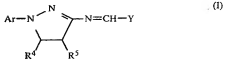
(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R^4 and R^5 are each the same or different and are each selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

12. A method for the prevention or treatment of inflammation in a mammal in need thereof comprising the administration to said mammal of 3-salicylideneamino-1-(3-trifluoromethylphenyl)-2-pyrazoline or a pharmaceutically acceptable salt thereof.

13. The method of claim **12** in which the mammal is a human.

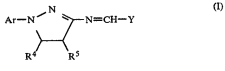
14. A method for the prophylaxis or treatment of pain in a mammal in need thereof, including man, comprising the administration to said mammal of a non-toxic, effective analgesic amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof:



(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R^4 and R^5 are each the same or different and are each selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

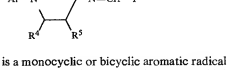
15. A method of inhibiting the lipoxygenase or cyclooxygenase pathways of arachidonic acid metabolism in a mammal in need thereof comprising the administration of an effective inhibitory amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo-substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R_4 and R_5 are each the same or different and are each selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

16. A method for the prophylaxis or treatment of pyresis in a mammal in need thereof, including man comprising the administration to said mammal of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

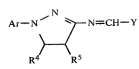


(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one

or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R^4 and R^5 are each the same or different and are selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

17. A method for the prophylaxis or treatment of asthma in a mammal in need thereof comprising the administration to a mammal of an antiasthmatic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein, Y is a monocyclic or bicyclic aromatic radical selected from phenyl, naphthyl, quinolyl, and pyridyl optionally substituted in any position of the ring by one or more substituent(s) selected from fluoro, chloro, bromo or iodo, nitro, carboxy, hydroxy, amino, monoalkyl substituted-amino, dialkyl substituted-amino, monohalo substituted-alkyl, dihalo substituted-alkyl, trihalo substituted-alkyl, alkyl, alkoxy, carboxyalkoxy, alkylsulphonyl, monohalo substituted-alkyl sulphonyl, dihalo substituted-alkyl sulphonyl and trihalo substituted-alkyl sulphonyl; R^4 and R^5 are each of the same or different and are each selected from hydrogen, alkyl, or Y as defined above; and Ar is selected from Y as defined above with the proviso that Ar is other than unsubstituted phenyl.

* * * * *

Exhibit E

United States Patent [19]

Terao et al.

[11] 4,393,075

[45] Jul. 12, 1983

[54] **QUINONE COMPOUNDS AND THEIR USE IN SUPPRESSING THE PRODUCTION OF SRS-A IN MAMMALS**

[75] Inventors: **Shinji Terao**, Toyonaka; **Mitsuru Shiraishi**, Suita; **Yoshitaka Maki**, Kyoto, all of Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.**, Osaka, Japan

[21] Appl. No.: **248,042**

[22] Filed: **Mar. 26, 1981**

[30] **Foreign Application Priority Data**

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Apr. 30, 1980 [JP] Japan 55-58464
Dec. 27, 1980 [JP] Japan 55-186622

[51] **Int. Cl.**[3] **A61K 31/12**; A61K 31/275; C07C 50/00

[52] **U.S. Cl.** ..... **424/304**; 260/396 R; 260/465 F; 424/308; 424/311; 424/317; 424/318; 424/320; 424/324; 424/331; 424/250; 560/106; 560/107; 560/255; 560/231; 562/466; 562/508; 564/180; 564/123; 568/811; 568/823

[58] **Field of Search** ..... 260/396 R; 424/331, 424/304

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,728,362 4/1973 Morimoto et al. ..... 260/396 R
4,139,545 2/1979 Morimoto et al. ..... 260/396 R

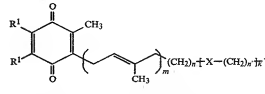
FOREIGN PATENT DOCUMENTS

53-20432 2/1978 Japan .

Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] **ABSTRACT**

New quinone compounds of the formula:



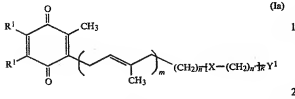
wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—; X is —CH=CH— or —C≡C—; Y^1 is hydrogen, hydroxyl, carboxyl, cyano, acyloxy or —COZ in which Z is amino which may be substituted; m is zero or an integer of 1 to 3; n is zero or an integer of 1 to 10; n' is an integer of 1 to 5; k is an integer of 1 to 3; and when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the $—X—(CH_2)_{n'}$ group; and their hydroquinone forms and salts, have useful physiological activities such as antiasthmatic, antiallergic and blood-pressure decreasing activities.

14 Claims, No Drawings

QUINONE COMPOUNDS AND THEIR USE IN SUPPRESSING THE PRODUCTION OF SRS-A IN MAMMALS

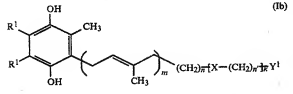
The present invention relates to novel quinone compounds which are of value as drugs or intermediates for them.

More particularly, the compounds of the present invention are quinone compounds of the formula:


(Ia)

wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH═CH—CH═CH—; X is —CH═CH— or —C≡C—; Y^1 is hydrogen, hydroxyl, carboxyl, cyano, acyloxy or —COZ in which Z is amino which may be substituted; m is zero or an integer of 1 to 3; n is zero or an integer of 1 to 10; n' is an integer of 1 to 5; k is an integer of 1 to 3; and when k is 2 or 3, each occurrence of the n' is optionally variable within the range of 1 to 5 in —X—$(CH_2)_{n'}$ group and their hydroquinone forms, and pharmaceutically acceptable salts thereof.

The hydroquinone forms of the above quinone compounds (Ia) are represented by the formula:

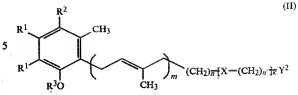

(Ib)

wherein all the symbols are as defined above.

With regard to the above-mentioned formulas (Ia) and (Ib), as examples of the substituted amino group represented by Z in —COZ, there may be mentioned mono- or di-C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino) and 5- or 6-membered cyclic amino (e.g. pyrrolidinyl, piperidino, piperazinyl). Said piperazinyl group may have a substituent such as C_{1-4} alkyl (e.g. methyl, ethyl) or C_{7-10} aralkyl (e.g. benzyl, 3,4,5-trimethoxybenzyl) on the nitrogen atom at its 4-position. A preferred embodiment as Z is amino, mono- or di-C_{1-4} alkylamino, pyrrolidinyl, piperidino or piperazinyl, said piperazinyl being unsubstituted or substituted at the N atom of its 4-position by C_{1-4} alkyl, benzyl or 3,4,5-trimethoxybenzyl.

Examples of the acyloxy group represented by Y^1 include C_{2-4} alkanoyloxy (e.g. acetyloxy, propionyloxy), benzoyloxy, etc.

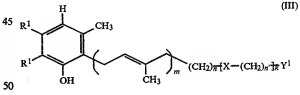
The compounds (Ia) and (Ib) of the present invention can be produced by subjecting a compound of the formula:


(II)

wherein R^1, X, m, n, n' and k are as defined above; R^2 is hydrogen, methoxy, methoxymethyloxy, 2-tetrahydropyranyloxy or 2-tetrahydrofuryloxy; R^3 is methyl, methoxymethyl, 2-tetrahydropyranyl or 2-tetrahydrofuryl; Y^2 has the same meaning as Y^1 defined above, or is 2-tetrahydropyranyloxy or 2-tetrahydrofuryloxy, to a reaction for removal of the protective group, and then, if necessary, subjecting the deprotected compound to oxidation.

With regard to the above-mentioned formula (II), the 2-tetrahydropyranyloxy and 2-tetrahydrofuryloxy groups in Y^2 are converted into the hydroxyl groups through the protective group removal reaction, while other groups correspond to those in Y^1, respectively.

As the protective group removal reaction for the compound (II), there may be mentioned, by way of example, hydrolysis, oxidation for removal of the protective group, etc. Such hydrolysis is normally conducted in an aqueous organic solvent (e.g. acetone, acetonitrile, tetrahydrofuran, 1,2-dimethoxyethane, ethanol, methanol) in the presence of an acid catalyst (e.g. sulfuric acid, camphorsulfonic acid, p-toluenesulfonic acid). The reaction temperature varies depending on the type of the protective groups to be removed and, normally, the reaction is conducted at a temperature within the range of 0° C. to 70° C. The protective groups, which can be easily removed by the hydrolysis reaction, include methoxymethyl, 2-tetrahydropyranyl, 2-tetrahydrofuryl and others. As the compound to be obtained by the hydrolysis, there may be mentioned the above hydroquinone forms (Ib) or phenol compounds of the formula:


(III)

wherein each of the symbols is as defined above. The compounds (III) possess pharmacological activities similar to those of the compounds (Ia) and (Ib).

The oxidation reaction for removal of the protective group of the compound (II) is conducted by using, for example, a divalent silver compound (e.g. AgO) or cerium compound [e.g. $Ce(NH_4)_2(NO_3)_6$]. Thus, the compound (II) in water or an aqueous organic solvent (e.g. dioxane, acetonitrile) is reacted with the use of AgO in the presence of nitric acid or $Ce(NH_4)_2(NO_3)_6$ in the presence of trimellitic acid-pyridine or pyridine-2,6-dicarboxylic acid or its N-oxide, pyridine-2,4,6-tricarboxylic acid or its N-oxide, etc. The reaction temperature is normally in the range of about 0° C. to 30° C. Said oxidative protective group removal reaction is particularly suited for removal of two methoxy groups situated in the para positions, and permits simulta-

neously removal of the protective groups and production of the quinone compound (Ia).

The hydroquinone compounds (Ib) and phenol compounds (III), which are formed when a hydrolysis reaction is employed as the reaction for removal of the protective group, can be converted into the quinone compounds (Ia) by subjecting them further to an oxidation reaction, if necessary. Such oxidation is normally carried out in a suitable aqueous organic solvent (e.g. dimethylformamide, acetonitrile, dioxane, tetrahydrofuran, methanol, ether, 1,2-dimethoxyethane) with the use of a mild oxidizing agent (e.g. Fremy's salt [.O—N(-$SO_3K)_2$], ferric chloride, silver oxide, air). The reaction temperature is normally in the range of about 0° C. to 30° C.

The quinone compound (Ia) where the radical represented by Y^1 is a —COZ group can also be produced by subjecting to the per se known amidation reaction (e.g. the reaction with the use of dicyclohexylcarbodiimide or the active ester method utilized in the peptide synthesis) the quinone carboxylic acid compound (Ia) where Y^1 is a carboxyl group.

Also, the objective compound (Ia) or (Ib) of the present invention where the radical represented by X is —CH=CH— can be produced by catalytic partial reduction of the compound (Ia) or (Ib), where the radical represented by X is —C≡C—, in the presence of Lindlar catalyst. Reduction with Lindlar catalyst is conducted in a solvent such as methanol, ethanol and ethyl acetate after adding quinoline in an amount of about 1/10 to 2 times that of the catalyst to adjust the catalytic activity. The double bond resulting from said partial reduction is mainly a cis-olefin bond

The quinone compounds (Ia) and their hydroquinone forms (Ib) thus produced can be isolated and collected by separation and purification procedures per se known (e.g. chromatography, distillation, crystallization) and others.

Furthermore, the quinone compounds (Ia) and hydroquinone compounds (Ib) of the present invention should be considered as pharmacologically equivalent, because they are convertible into each other under physiological conditions. Generally, the hydroquinone compounds (Ib) are chemically susceptible to oxidation and are preferably handled as the quinone compounds (Ia). The hydroquinone compounds (Ib) can be converted into the stable form such as the above-mentioned compounds (II) by introducing the protective group into the hydroxyl group by way of a reaction known per se (e.g. etherification, benzylation, acylation).

The compounds (Ia) and (Ib) of the present invention exert profound effect upon the metabolic pathway for polyunsaturated fatty acids (PUFA) such as linoleic acid, linolenic acid, dihomo-γ-linolenic acid, arachidonic acid and eicosapentaenoic acid, particularly the metabolic pathways involving lipoxygenase and cyclooxygenase. For example, the compounds suppress production of SRS-A (slow reacting substance of anaphylaxis), the substance known to cause immediate allergy, and simultaneously inhibit production of 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and 5-hydroxyeicosatetraenoic acid (5-HETE).

5-HPETE is one of hydroperoxy-fatty acids produced from arachidonic acid by lipoxygenase in human polymorphonuclear leukocytes, rat mastocytes, etc. and an important intermediate for SRS-A, as well [Proc. Natl. Acad. Sci., vol. 76, pp. 4275 (1979)]. The objective compounds (Ia) or (Ib) of the present invention, by suppressing production of 12-hydroperoxyeicosatetraenoic acid (12-HPETE) liberated for example from human blood platelets, leukocytes and mastocytes, and rat peritoneal cells, and by simultaneously inhibiting liberation of various hydroperoxy-fatty acids produced from PUFA, get involved in the defense in living tissues and cells against hydroperoxy-fatty acids, and are useful for improvement of the prostaglandin-thromboxane metabolism. For example, they are of use in preventing the prostaglandin-I_2 (PGI_2) synthatase from being inactivated by hydroperoxy-fatty acids. In addition, the compounds (Ia) and (Ib) of the present invention inhibit autoxidation of arachidonic acid in the concentration of near 1 μM.

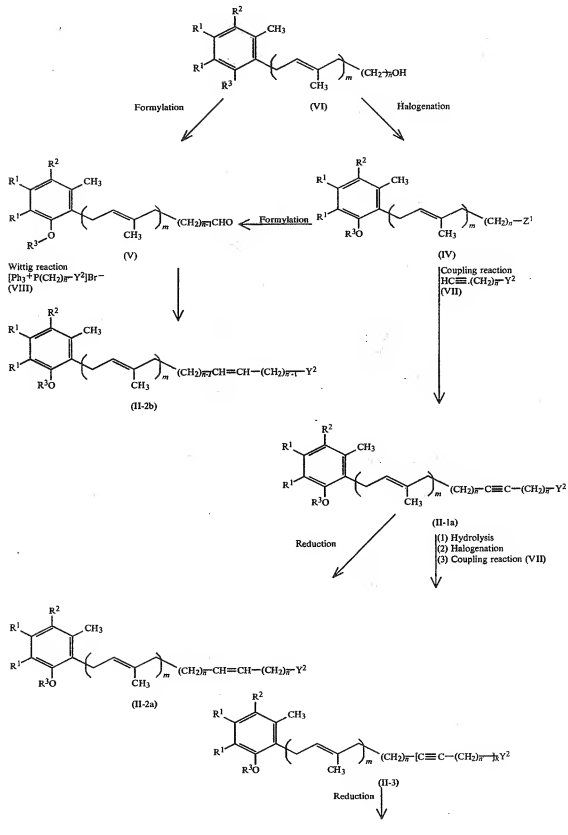
Based on their improvement of the metabolism of PUFA, particularly their inhibitory action on production of hydroperoxy-fatty acids, namely anti-oxidizing activity, the compounds (Ia) and (Ib) of the present invention exhibit in mammals various physiological actions such as antiasthmatic, antiallergic, blood-pressure decreasing, arteriosclerosis-improving, atherosclerosis-improving, platelet-aggregation improving, renal-, cerebral- and coronary-circulation improving, anti-digestive-tract-ulcer, diuretic, immuno-regulatory and bacterial-infection defending actions. Thus, they are of value as drugs, such as an antiasthmatic agent, antiallergic agent, antihypertensive agent, antiulcer agent, diuretic agent, antithrombotic agent, cerebral-circulation improving agent, coronary artery improving agent, immuno-regulating agent, bacterial-infection defense promoting agent and prostaglandin-thromboxane metabolism improving agent, in the treatment or prophylaxis of, bronchial asthma, allergosis, hypertension, peptic ulcer, cerebral thrombosis, ischemic myocardial infarction, coronary artery disorders, atherosclerosis, immuno-deficiency, disorder of regulation in prostaglandin- and thromboxane-biosynthesis, etc. In particular, the present compounds are useful as antiasthmatic, antiallergic, antiulcer and cerebral-circulation improving agents.

The compounds of the present invention are low in toxicity and can be safely administered either orally or parenterally, as such or as a pharmaceutical composition [e.g. tablets, capsules (inclusive of soft capsules and microcapsules), solutions, injections and suppositories] formed by mixing them with pharmaceutically acceptable carriers, excipients, etc. conventional per se. The dosage varies depending upon type of hosts, administration route, symptom, etc. In the case of oral administration to patients with hypertension or bronchial asthma, they are given suitably in a single dose within the range of, normally about 0.2 mg/kg to 25 mg/kg of body weight, preferably about 0.5 to 10 mg/kg of body weight, 1 to 3 times daily.

In cases in which the compounds (Ia) and (Ib) of the present invention are employed as the above drugs, the quinone compounds (Ia) are generally preferable in terms of stability, etc. Among (Ia), the compound where R^1 is methyl or methoxy and X is —C≡C— is preferred in the case of the inhibitory action on the production of SRS-A, and the compound where R^1 is methoxy is preferable in the case of antiulcer action. In

both of the above cases, preferably, Y^1 is hydroxyl, and m is zero or 1, while n, n' and k are integers of 1 to 4, 1 to 3 and 1 to 2, respectively.

The starting compounds (II) useful in the present invention can be produced, for example, by the following procedure:



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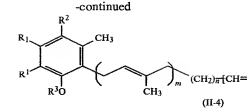


(II-4)

[wherein Ph is phenyl, Z^1 is halogen (e.g. Br, I) and other symbols are as defined above]

The starting compounds (VI) in the present invention may be prepared by the production methods described for example in the Japanese Unexamined Patent Publication Nos. 128932/1976 and 7737/1981 (Application No. 84291/1979), and Japanese Patent Application No. 49433/1980.

The alcohol compound (VI) can be converted to the corresponding halogen compound (IV) or aldehyde compound (V) by halogenating or formylating it. The halogen compound (IV) can be derived by treating the alcohol compound (VI) with phosphorus tribromide or treating a sulfonyl ester form of the alcohol compound (VI) with a halide.

The bromination reaction of the alcohol compound (VI) is conducted in dichloromethane, chloroform, ether, isopropyl ether or tetrahydrofuran at a temperature within the range of 0° C. to 70° C., with the use of $\frac{1}{3}$ to 1 equivalent mole of phosphorus tribromide.

The production of the halogen compound (IV) via sulfonyl ester is carried out by way of the following reaction: the alcohol compound (VI), by the action of methanesulfonyl chloride or p-toluenesulfonyl chloride in an organic solvent (e.g. methylene chloride, chloroform, ether) in the presence of an organic base (e.g. triethylamine, pyridine), is derived into the corresponding methanesulfonyl or p-toluenesulfonyl ester, which, on treating at room temperature or under heating in a halogen compound (e.g. sodium chloride, sodium bromide, potassium bromide, sodium iodide, potassium iodide) and an organic solvent (e.g. acetone, dimethylformamide, dimethylsulfoxide), can yield the corresponding halogen compound (IV).

The aldehyde compound (V) can be derived by oxidizing the alcohol compound (VI) or halogen compound (IV). In the oxidation of the alcohol compound (VI), for example, the reaction with sulfur trioxide-pyridine complex and triethylamine in pyridine-anhydrous chromic acid or dimethylsulfoxide and the like are employed, and, in the case of the halogen compound (IV), for example, treatment with silver tetrafluoroborate ($AgBF_4$)-triethylamine in dimethylsulfoxide affords the aldehyde compound (V).

The halogen compound (IV) or aldehyde compound (V) thus obtained is converted into the compound (II-1a) or (II-2b) by subjecting it to a coupling reaction or the Wittig reaction.

The coupling reaction with the acetylene compound (VII) is conducted by the action of the halogen compound (IV) in liquid ammonia or an organic solvent (e.g. tetrahydrofuran, hexamethylphosphoramide, dimethylformamide, dimethylsulfoxide) in the presence of sodium amide or lithium amide, or in an organic solvent (e.g. diethyl ether or tetrahydrofuran) in the presence of ethyl magnesium bromide and a catalytic amount of copper ion, thereby forming the compound (II-1a).

The acetylene compound (VII), which is employed in the coupling reaction, includes, by way of example, 5-hexyne carboxylic acid, 1-hydroxypent-4-yne, 1-hydroxybut-3-yne, propargyl alcohol and their tetrahydropyranyl ethers.

The coupling reaction in liquid ammonia or an organic solvent is normally conducted under an inert gas atmosphere at a temperature of about −30° C. to −70° C., while the Grignard type coupling reaction in an organic solvent is carried out at room temperature or at the boiling point of the solvent, using a copper catalyst (e.g. cuprous cyanide, cuprous bromide, cuprous iodide). The reaction mixture is subjected to isolation and purification by per se conventional procedures (e.g. solvent extraction silica-gel chromatography) to give the compound (II-2b).

The compound (II-1a) can be derived by the reaction of the aldehyde compound (V) with the Wittig reagent (VIII). As the Wittig reagent, there may be mentioned, for example, $[Ph_3P^+(CH_2)_4COOH]Br^-$, $[Ph_3P^+(CH_2)_5—COOH]Br^-$, etc., while as the solvent, there may be mentioned benzene, toluene, ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, dimethylsulfoxide, etc., either solely or as mixed solvents. The reaction is conducted under an inert gas atmosphere and in the presence of a basic compound (e.g. n-butyllithium, methyllithium, sodium hydride, etc.), normally at −10° C. to +40° C. After the completion of the reaction, the compound (II-2b) is obtained by separation and purification of the reaction product by a conventional procedure.

The compound (II-1a) or (II-2b) produced by the above procedure can be utilized as the starting compound (II) itself, but can also be converted into other starting compounds (II) by allowing the reaction to proceed further.

Thus, among the compounds (II-1a) obtained in the above coupling reaction step, the compound where Y^2 is a hydroxyl group can be subjected to the above-mentioned halogenation reaction to thereby led to the corresponding halide which can form the longer acetylene compound (II-3) by the similar coupling reaction with the above-mentioned acetylene compound (VII). If necessary, the similarly repeated coupling reaction can also afford an even longer acetylene compound (II-3). In the case of the repeated coupling reaction, n' in the acetylene compound (VII) can be changed to any integer of 1 to 5. In cases in which the compound of the formula (II-3) where k is not less than 2 and n' is 1 is produced, preferred is the coupling reaction in tetrahydrofuran or diethyl ether with the use of Grignard reagent.

The compound (II-3) thus obtained can be utilized as the starting compound (II) itself, and the compounds (II-1a) and (II-3) can be converted to the olefin compound (II-2a) or (II-4) by partial reduction of the acetylene bond.

The partial reduction is, for example, by means of catalytic reduction with the Lindlar catalyst or partial

reduction with lithium aluminum hydride. The reduction with the Lindlar catalyst can be conducted under the same conditions as described above. Reduction with lithium aluminum hydride is carried out by a reaction under reflux in a solvent of ether or tetrahydrofuran under an inert gas atmosphere.

The geometrical configuration of the di-substituted double bond in the olefin compounds (II-2a) and (II-4) as obtained in the above reduction is the cis-oriented olefin bond in the case of the reduction with the Lindlar catalist, while it is the trans-oriented olefin bond in the case of the reduction with lithium aluminum hydride.

The compounds (II-1a), (II-2a), (II-2b), (II-3) and (II-4) as obtained in the above reaction are all utilizable as the starting compound (II) themselves and, if necessary, can be converted to e.g. the cyano and amide compounds (II) by way of the conventional, known reactions such as protective-group removal reaction, reaction of converting a halogen compound into a nitrile group, esterification or amidation reaction of a carboxyl compound.

The production of the starting compound (VI) by the procedure described in Japanese Patent Application No. 49433/1980 will be explained hereinafter in detail.

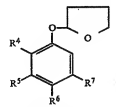
The application relates to a process for producing a phenol compound having a tetrahydrofur-2-yl group at its ortho position characterized in that said process comprises acting an acid catalyst under anhydrous conditions on a tetrahydrofur-2-yl ether of a compound having a phenolic hydroxyl group with at least one of the ortho positions being unsubstituted.

As the acid catalyst in the above process, there may be mentioned organic sulfonic acids such as p-toluenesulfonic acid, camphorsulfonic acid and methanesulfonic acid, trifluoroacetic acid, sulfuric acid, boron trifluoride diethyl ethereate and the like, and the amount of these to be used is in the range of about 1/100 to 1/5 equivalent, preferably about 1/30 to 1/10, against an ether compound as the starting compound.

The reaction is carried out under anhydrous conditions, whereby as the solvent for the reaction, normally, use is made of anhydrous solvents such as dichloromethane, chloroform, toluene, benzene and isopropyl ether. The reaction temperature is normally in the range of room temperature to about 70° C. The reaction is desirably carried out under an atmosphere of an inert gas, and the reaction temperature varies with types of compounds to be reacted but is normally in the period of 1 to 10 hours. The objective compound produced in the reaction solution can be easily isolated by means of conventional separation and purification procedures (e.g., silica gel chromatography, distillation under reduced pressure) after neutralization of the acid catalyst.

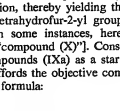
The above-mentioned process is applied to the tetrahydrofur-2-yl ethers of compounds having a phenolic hydroxyl group with at least one of the ortho positions being unsubstituted [in some instances, hereinafter referred to briefly as "compound (IX)"], as described above. Such compounds having a phenolic hydroxyl group, which are not limited to simple phenol and its derivatives, mean the phenols as taken in a broad sense including for example catechol, pyrogallol, resorcinol, catecholamine derivatives, 5-hydroxytryptamine (serotonin), 5-hydroxyindole, etc. The reaction for etherification of such compounds with 2,3-dihydrofuran in the presence of an acid catalyst or with 2-chlorotetrahydrofuran in the presence of a base can afford the tetrahydrofur-2-yl ether compounds (IX). As the acid catalyst may be mentioned the same acid catalysts as those mentioned above, and their sufficient amount to be used is in the range of about 1/500 to 1/100 equivalent against a starting compound. In the case of the reaction with 2,3-dihydrofuran, the reaction temperature is normally in the range of 0° to 40° C. In this case, the acid catalyst is further added after the completion of the etherification reaction, while the reaction temperature is increased, if necessary, whereby the rearrangement can be consecutively carried out. By employing the catalyst amount and reaction temperature for the rearrangement reaction from the very beginning of the etherification, furthermore, the etherification and rearrangement can be carried out in one step as well. As examples of the base being useful in the etherification with 2-chlorotetrahydrofuran, there may be mentioned triethylamine, pyridine, sodium hydride, etc. As the solvent for the reaction, use is made of dichloromethane, chloroform, dimethylformamide, dimethylacetamide, etc.

As one specific example of the above compound (IX), there may be mentioned, by way of example, ether compounds of the formula:


(IXa)

wherein R^4, R^5, R^6 and R^7 are independently hydrogen, hydroxyl, methyl or methoxy; any two neighboring groups of R^4, R^5, R^6 and R^7 jointly represent —CH=CH—CH=CH—.

In the above process, the tetrahydrofur-2-yl group of the compound (IX) undergoes rearrangement into the position adjacent to the phenolic hydroxyl group or the ortho position, thereby yielding the objective phenols having a tetrahydrofur-2-yl group in the said ortho position [in some instances, hereinafter referred to briefly as "compound (X)"]. Consequently, utilization of the compounds (IXa) as a starting compound, for example, affords the objective compounds of the phenols of the formula:


(Xa)

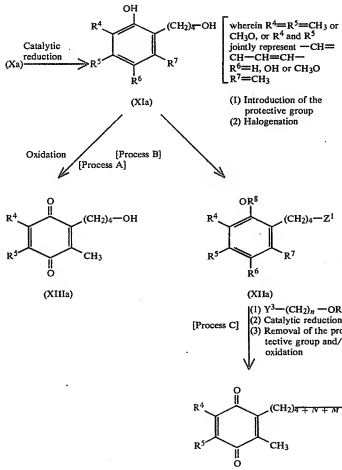
wherein all the symbols are as defined above.

According to the process mentioned above, the tetrahydrofur-2-yl group can be introduced into the ortho position of phenols in very high yields and selectively under mild reaction conditions.

The compounds (X) themselves, as produced by the present invention, are novel compounds, and are of value as intermediates for producing various drugs (e.g., catecholamines, naphthoquinones, benzoquinones, etc.). Thus, the tetrahydrofur-2-yl group in the ortho position of the compounds (X), by the catalytic reduction lead-

ing to ring-opening, can be easily converted into a 4-hydroxybutyl group, whereupon the resulting 4-hydroxybutyl group, when, for example, halogenated to a reactive halogenobutyl group becomes susceptible of the extension of its butyl chain, thus permitting the favorable production of varieties of valuable phenol derivatives. The ring-opening reaction by the catalytic reduction is carried out, with the use of acid catalyst (e.g., sulfuric acid, perchloric acid, etc.) and reducing catalyst (e.g., palladium, platinum, etc.), in a solvent such as acetic acid and ethyl acetate under applied pressure and warming. The halogenation is conducted, for example, by producing the corresponding sulfonyl ester with methanesulfonyl chloride or p-toluenesulfonyl chloride, followed by treating with sodium bromide or sodium iodide by a conventional procedure. In these reactions, if necessary, the phenolic hydroxyl group may be protected in advance and subjected to reaction.

By way of example, the following are the routes of the phenols (Xa) to valuable drug compounds or the compounds (VI)



[wherein R^8 is a protective group for the phenolic hydroxyl group; R^9 is a protective group for the alcoholic hydroxyl group; Z^1 is halogen (e.g., Br or I), $—P^+(C_6H_5)_3I^-$ or $—P^+(C_6H_5)_3Br^-$; Y^3 is formyl, CH=C- or p-toluenesulfonyl; N is an integer of 0 to 18; M is an integer of 0 to 2, with (N+M) representing an integer of 1 to 18].

The oxidation in the step A as described above is carried out with the use of a mild oxidizing agent (e.g., Fremy's salt, silver oxide, ferric chloride, etc.). The introduction of a protective group in the step B is conducted by introducing a group normally employed for protecting the phenolic hydroxyl group such as methyl, benzyl, methoxymethyl and tetrahydropyranyl groups by procedures known per se. The halogenation in the step B is carried out by the procedure described hereinbefore. The reaction of (XIIa) with (XIV) in the step C is carried out by the Wittig reaction in the case of aldehydes utilized as (XIV) and by the condensation reaction under acidic conditions in the case of acetylenes or sulfones used as (XIV), respectively. In cases in which aldehydes (XIV) are utilized, M is 1, while in the case of acetylenes, M is 2, and in the case of sulfones, M is 0. The olefin compounds or acetylene compounds obtained by these reactions can be derived into the objective quinone compounds (XIIIb) by the catalytic reduction by means of conventional procedures, followed by removal of protective group and/or by oxidation. Further, the sulfone compounds can be derived into (XIIIb) by desulfonation under basic conditions followed by treatment of the resulting olefin compounds in the same manner as described above.

The above compounds (XIIIa) and (XIIIb) are, for example of value as immunostimulating agent, tissue metabolism activator (therapeutic agents for cerebral

circulation disturbance, cardiac insufficiency, hypertension, etc.) and the like [refer to U.S. Pat. No. 4,139,545 (Japanese Patent Unexamined Publication No. 128932/1967), European Patent Publication No. 21841 and Japanese Patent Application No. 171125/1979].

The compounds (XIa) and (XIIa) are included in the scope of the compounds (VI) and (IV) mentioned hereinbefore and are useful as intermediates for the production of the present compounds (Ia) and (Ib).

The following examples illustrate the present invention in more detail, but they are not intended to limit its scope. The symbols in the tables shown below designate the following chemical formulas, respectively.

Symbol	Formula	Symbol	Formula
Q		Q_1	
Q_2		Q_3	
E		E_1	
K		K_1	

EXPERIMENTAL EXAMPLE

The inhibitory action on SRS-A production and release

The actions of the objective compounds of the present invention on SRS-A production and release were determined in accordance with the method of Orange and Moore [J. Immunol., vol. 116, pp. 392 (1976)]. To lung fragments of guinea-pigs (male and female Hartley strain, weighing 300 to 350 g) sensitised with egg albumin as the antigen was added the objective compound of the present invention, simultaneously with the antigen, and the amount of SRS-A produced and released as a consequence was assayed by the method of Brocklehurst (J. Physiol., vol. 151, pp. 416-435, 1960). The results as shown in Table 1 indicate that the compounds of the present invention strongly inhibit the production and release of SRS-A in lower concentrations and that they are outstandingly excellent as compared with the known inhibitors of SRS-A production such as 5,7,11,14-eicosatetraynoic acid (ETYA) and sodium baicalein phosphate (BPS).

TABLE 1

The inhibitory action on SRS-A production and release

Tested compound	Concentration (μM)	Inhibitory effect on SRS-A production (%)
	1	26.3 ± 11.3
	10	78.9 ± 1.1
	1 10	21.5 ± 5.4 88.8 ± 5.7
	10	74.7 ± 2.5
	10	80.1 ± 3.1
	10	77.3 ± 1.4
	1 10	15.7 ± 4.6 69.3 ± 7.1
	10	70.7 ± 10.4
	10	63 ± 7.2
	1 10	53.8 ± 6.3 77.7 ± 4.2
	1 10	25.3 ± 8.7 61.6 ± 5.4
	1 10	20.2 ± 9.6 57.3 ± 12.7
ETYA	10	56.9 ± 5.9
BPS	100	50.8 ± 10.7

EXAMPLE 1

In a mixed solvent of acetonitrile (40 ml) and water (20 ml) were dissolved the compound produced in Reference Example 2 (II, $R^1=R^2=OCH_3$, $R^3=CH_3$, m=0, n=4, X=—C≡C—, n'=3, Y^2=OH, k=1, 3.00 g, 8.57 mmole) and 2,6-dicarboxypyridine N-oxide (4.70 g, 8.57×3 mmole), and the solution was stirred under cooling with ice. An ice-cooled solution of ceric ammonium nitrate (14.1 g, 8.57×3 mmole) in 50% aqueous acetonitrile (60 ml) was added dropwise to the solution over a period of 30 minutes, followed by stirring under the same conditions for 30 minutes and at room temperature for 30 minutes. After the completion of the reaction, insolubles were filtered out, and the acetonitrile was distilled off under reduced pressure. To the residue were added isopropyl ether (100 ml) and water (20 ml) for extraction, and the organic layer was washed with saturated sodium bicarbonate and aqueous sodium chloride successively, and dried (over $MgSO_4$), followed by distilling off the organic solvent under reduced pressure. The residue was chromatographed on a column of silica gel developing with isopropyl ether:ethyl acetate (98:2 to 95:5) to give 2,3-dimethoxy-5-methyl-6-(9-hydroxynon-5-ynyl)-1,4-benzoquinone (Ia, $R^1=OCH_3$, m=0, n=4, X=—C≡C—, n'=3, k=1, Y^1=OH, 2.24

g 82%). As to its physical properties, refer to Table 2 (The same shall apply hereinafter).

EXAMPLES 2 TO 15

By the procedure of Example 1, there were obtained the compounds as shown in Table 2.

EXAMPLE 16

In dioxane (10 ml) was dissolved the compound produced in Reference Example 5 (II, $R^1=R^3=CH_3$, $R^2=OCH_3$, m=0, n=4, X=—C≡C—, n'=3, Y^2=OH, k=1, 636 mg, 2.0 mmole). After silver oxide (AgO, 1.0 g, 8 mmole) was added to the solution, 6 N nitric acid (2.0 ml) was added to the mixture under stirring at room temperature, followed by allowing the reaction to proceed for 30 minutes. Water (50 ml) was added, and the product was extracted with ethyl acetate. The organic layer was washed with water, dried (over $MgSO_4$) and concentrated. The residue was chromatographed on silica gel developing with isopropyl ether:ethyl acetate (98:2) to give 2,3,5-trimethyl-6-(9-hydroxynon-5-ynyl)-1,4-benzoquinone (Ia, $R^1=CH_3$, m=0, n=4, X=—C≡C—, n'=3, k=1, Y^1=OH, 520 mg, 90%).

EXAMPLES 17 TO 20

By the procedure of Example 16, there were obtained the compounds as shown in Table 2.

EXAMPLE 21

In acetone (25 ml) was dissolved the compound produced in Reference Example 15 (II, $R^1=OCH_3$, $R^2=OCH_2OCH_3$, $R^3=CH_2OCH_3$, m=1, n=1, $X=\overset{H}{>}=<\overset{H}{}$, n'=4, k=1, Y^2=COOH, 2.40 g, 5.0 mmole) and, after the addition of 2 N sulfuric acid (5.0 ml), the solution was stirred under reflux at 70° C. for 1 hour. After the reaction solution was cooled, 1 M aqueous ferric chloride solution (10.0 ml) was added, followed by stirring at room temperature for 30 minutes. After the completion of the reaction, the acetone was distilled off under reduced pressure, and the product was extracted by adding ethyl acetate (100 ml) and water (50 ml). The organic layer was washed with aqueous sodium chloride solution, dried (over $MgSO_4$) and concentrated. The residue was chromatographed on a column of silica gel developing with isopropyl ether:ethyl acetate (98:2) to give 2,3-dimethoxy-5-methyl-6-[11-carboxy-3-methyl-(E,Z)-2,6-undecadienyl]-1,4-benzoquinone (Ia, $R^1=OCH_3$, m=1, n=1, $X=\overset{H}{>}=<\overset{H}{}$, n'=4, k=1, 2.17 g, 88%).

EXAMPLE 22

By the procedure of Example 21, there was obtained the compound as shown in Table 2.

EXAMPLE 23

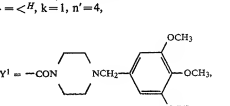
In ethyl acetate (10 ml) was dissolved the compound produced in Example 7 (Ia, $R^1=CH_3$, m=0, n=4, X=—C≡C—, n'=1, k=2, Y^1=OH, 0.30 g, 1.0 mmole) and, after the Lindlar catalyst (60 mg) and quinoline (10 μl) were added to the solution, catalytic reduction was carried out at room temperature. At the time when 2.5 molar hydrogen was absorbed, the reaction was suspended. The catalyst was filtered out, and the ethyl acetate solution was washed with a 5% aqueous phosphoric acid solution (5 ml) and an aqueous sodium chloride solution (5 ml), successively, followed by concentrating the organic layer. The residue was dissolved in tetrahydrofuran (6 ml) and, after the addition of a 1 M aqueous ferric chloride solution, the mixture was stirred at room temperature for 30 minutes. The tetrahydrofuran was distilled off under reduced pressure, and the product was extracted by adding isopropyl ether (30 ml) and water (10 ml) to the residue. The organic layer was washed with aqueous sodium chloride, dried (over $MgSO_4$) and concentrated by distilling off the solvent under reduced pressure. The residue was chromatographed on a column of silica gel developing with isopropyl ether:ethyl acetate (98:2) to give 2,3,5-trimethyl-6-[10-hydroxy(Z,Z)-5,8-decadienyl]-1,4-benzoquinone (Ia, $R^1=CH_3$, m=0, n=4, $X=\overset{H}{>}=<\overset{H}{}$, n'=1, k=2, Y^1=OH, 0.24 g, 80%).

EXAMPLES 24 TO 26

By the procedure of Example 23, there was obtained the compound as shown in Table 2.

EXAMPLE 27

In acetonitrile (10 ml) were dissolved the compound produced in Example 15 (Ia, $R^1=OCH_3$, m=1, n=1, $X=\overset{H}{>}=<\overset{H}{}$, n'=4, k=1, Y^1=COOH, 0.78 g, 2.0 mmole) and N-hydroxysuccinimide (0.25 g, 2.2 mmole), and the solution was stirred under cooling with ice. After dicyclohexylcarbodiimide (0.45 g, 2.2 mmole) was added to the solution, the mixture was cooled with ice for 30 minutes and stirred at room temperature for 1.5 hours. Then, N-(3,4,5-trimethoxybenzyl)-piperazine (0.59 g, 2.2 mmole) was added, and the mixture was stirred at room temperature for 1 hour. After the completion of the reaction, dicyclohexyl urea was filtered out, and the acetonitrile was distilled off under reduced pressure. To the residue were added ethyl acetate (50 ml) and water (30 ml) for extraction, and the organic layer was washed with aqueous sodium bicarbonate solution and aqueous sodium chloride solution, successively, and dried (over $MgSO_4$), followed by distilling off the solvent. The residue was chromatographed on a column of silica gel developing with isopropyl ether:ethyl acetate (10:1) to give 2,3-dimethoxy-5-methyl-6-[[3-methyl-11-[N-((N'-(3,4,5-trimethoxybenzyl)-piperazinocarbonyl))-(E,Z)-2,6-undecadienyl]]]-1,4-benzoquinone (Ia, $R^1=OCH_3$, m=1, n=1, $X=\overset{H}{>}=<\overset{H}{}$, k=1, n'=4,



1.08 g, 85%).

EXAMPLES 28 TO 29

By the procedure of Example 27, there was obtained the compound as shown in Table 2.

EXAMPLE 30

In methanol (50 ml) was dissolved the compound produced in Reference Example 11 (II, $R^1=R^2=OCH_3$, $R^3=CH_3$, m=1, n=2, X=—C≡C—, n'=2, k=1,

2.07 g, 3.98 mmole), and camphorsulfonic acid (0.1 g) was added to the solution, followed by refluxing for 1 hour. After the reaction solution was cooled, sodium bicarbonate (0.1 g) was added, and the solvent was distilled off under reduced pressure. The residue was dissolved in isopropyl ether (100 ml), and the organic layer was washed with water, dried (over magnesium sulfate) and concentrated under reduced pressure. The residue was chromatographed on silica gel developing with isopropyl ether:ethyl acetate (98:2) to give 2,3-dimethoxy-5-methyl-6-[10-hydroxy-3-methyl-7-yn-(2E)-decenyl]-1,4-hydrobenzoquinone (Ib, R^1=OCH_3, m=1, n=2, X=—C≡C—, n'=2, k=1, Y^1=OH, 1.29 g, 92%).

EXAMPLE 31

In a mixed solvent of acetonitrile (6 ml) and water (3 ml) were dissolved 5-methyl-1,2,3,4-tetramethoxy-6-(12-hydroxy-5,10-dodecadiynyl)benzene (II, 0.50 g, 1.29 mmole) and pyridine-2,6-dicarboxylic acid (0.65 g, 1.29×3 mmole), and the solution was stirred under cooling with ice, followed by adding dropwise and ice-cooled solution of ceric ammonium nitrate (2.12 g) in acetonitrile (4.5 ml) over a 15-minute period. The reaction was allowed to proceed under the same conditions for 15 minutes and further at room temperature for 15 minutes. After the completion of the reaction, the insolubles were filtered out, and the acetonitrile was distilled off under reduced pressure. By adding isopropyl ether (20 ml) and water (20 ml) to the residue, the product was extracted. The organic layer was washed with aqueous sodium bicarbonate solution and aqueous sodium chloride solution, successively, dried (over $MgSO_4$) and concentrated under reduced pressure, resulting in a residue. The residue was chromatographed on a column of silica gel developing with a mixed solvent of isopropyl ether and ethyl acetate to give 2,3-dimethoxy-5-methyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone (I, 0.42 g, 91%, oil).

EXAMPLE 32

Dioxane (15 ml) was added to 1,4-dimethoxy-2-methyl-3-[(12-hydroxy-5,10-dodecadiynyl)]naphthalene (II, 0.57 g, 1.5 mmole) and silver oxide (0.74 g, 6.0 mmole), and the mixture was stirred under cooling with ice. 6 N nitric acid (1.5 ml) was added to the mixture over a 5-minute period and, 5 minutes later, the ice bath was taken off, followed by stirring at room temperature for 30 minutes. Water (20 ml) was added to the reaction solution, and the dioxane was distilled off under reduced pressure. Ethyl acetate (50 ml) was added to the residue, and the insolubles were filtered out. The organic layer was separated out, washed with water and dried (over $MgSO_4$), followed by distilling off the solvent under reduced pressure. The crystals precipitated were recrystallized from isopropyl ether, thereby yielding the desired 2-methyl-3-(12-hydroxy-5,10-dodecadiynyl)-1,4-naphthoquinone (I, 0.47 g, 90%).

EXAMPLES 33 TO 35

By the procedure of Example 31, there were obtained the compounds as shown in Table 2.

TABLE 2

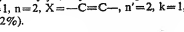
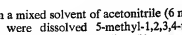
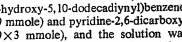
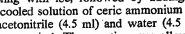
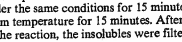
Ex. No.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
1		2	$C_{19}H_{24}O_5$ (320.39)	1.4–1.8(7H), 2.01(3H), 2.1–2.3(4H), 2.46(2H), 3.72(2H), 3.97(6H)
2		3	$C_{23}H_{32}O_5$ (386.49)	1.4–1.8(9H), 2.01(3H), 2.1–2.3(8H), 2.46(2H), 3.72(2H), 3.96(6H)
3		23	$C_{19}H_{22}O_5$ (330.39)	1.4–1.7(4H), 1.97(1H), 2.02(3H), 2.20(2H) 2.47(2H), 3.13(2H), 3.97(6H), 4.25(2H)
4		24	$C_{21}H_{26}O_5$ (358.44)	1.4–1.9(7H), 2.02(3H), 2.1–2.4(4H), 2.47(2H), 3.07(2H), 3.72(2H), 3.97(6H)
5		16	$C_{23}H_{34}O_5$ (390.53)	1.5–1.8(9H), 1.9–2.2 (8H), 2.00(3H), 2.45 (2H), 3.63(2H), 3.97 (6H), 5.3–5.5(4H)
6		14	$C_{19}H_{28}O_3$ (304.43)	1.3–1.7(9H), 1.9–2.2 (4H), 1.99(9H),2.47 (2H), 3.62(2H), 5.3–5.5(2H)
7		19	$C_{19}H_{22}O_3$ (298.39)	1.4–1.7(5H), 1.99(6H), 2.02(3H), 2.18(2H), 2.47(2H), 3.13(2H), 4.23(2H), m.p. 64–65° C.

TABLE 2-continued

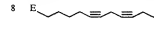
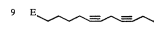
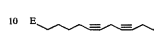
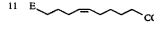
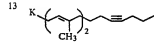
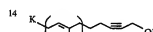
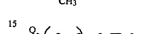
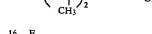
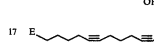
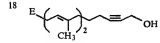
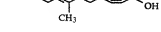
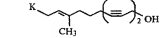
Ex. No.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
8		20	$C_{20}H_{24}O_3$ (312.41)	1.4–1.7(5H), 2.00(6H), 2.03(3H), 2.1–2.3(2H), 2.41(2H), 2.48(2H), 3.09(2H), 3.67(2H)
9		21	$C_{21}H_{26}O_3$ (326.44)	1.4–1.9(7H), 2.00(6H), 2.03(3H), 2.1–2.3(4H), 2.48(2H), 3.07(2H), 3.73(2H)
10		45	$C_{23}H_{25}NO_2$ (335.45)	1.4–1.9(6H), 2.0–2.3 (4H), 2.05(6H), 2.08 (3H), 2.3–2.7(4H), 3.15(2H), IR(neat): 2240 cm^{-1}
11		12	$C_{19}H_{26}O_4$ (318.42)	1.3–1.8(6H), 1.9–2.2 (4H), 1.99(9H), 2.2–2.6(4H), 5.3–5.5(2H)
12		22	$C_{22}H_{26}O_4$ (354.45)	1.4–1.9(6H), 1.99(6H), 2.02(3H), 2.1–2.3(4H), 2.39(2H), 2.47(2H), 3.08(2H)
13		25	$C_{29}H_{34}O_4$ (446.56)	1.57(3H), 1.78(3H), 2.18(3H), 2.0–2.5(8H), 3.35(2H), 5.0(2H), 7.5–8.2(4H)
14		7	$C_{26}H_{30}O_3$ (390.50)	1.57(3H), 1.78(3H), 2.18(3H), 2.0–2.5(8H), 3.35(2H), 4.23(2H), 5.0(2H), 7.5–8.2(4H)
15		8	$C_{24}H_{32}O_5$ (400.50)	1.57(3H), 1.72(3H), 2.0–2.5(8H), 3.97(6H), 4.23(2H), 5.0(2H)
16		5	$C_{18}H_{24}O_3$ (288.39)	1.4–1.9(7H), 2.00(6H), 2.02(3H), 2.1–2.3(4H), 2.47(2H), 3.73(2H)
17		6	$C_{21}H_{26}O_3$ (326.44)	1.4–1.8(7H), 2.00(6H), 2.03(3H), 2.1–2.3(6H), 2.47(2H), 4.21(2H), m.p. 53–54° C.
18		9	$C_{24}H_{32}O_3$ (368.50)	1.59(3H), 1.71(3H), 1.98(9H), 4.24(2H)
19		10	$C_{21}H_{22}O_3$ (322.39)	1.78(3H), 2.18(3H), 3.35(2H), 4.23(2H), 5.0(1H), 7.5–8.2(4H),
20		27	$C_{23}H_{24}O_3$ (348.42)	1.78(3H), 2.18(3H), 3.13(2H), 3.35(2H), 4.23(2H), 5.0(1H)
21		15	$C_{22}H_{30}O_6$ (390.48)	1.2–1.8(4H), 1.72(3H), 1.8–2.2(6H), 2.00(3H), 2.34(2H), 3.16(2H), 3.97(6H), 4.93(1H), 5.2–5.4(2H)
22		11	$C_{20}H_{26}O_5$ (346.43)	1.5–1.8(3H), 1.72(3H), 2.0–2.2(4H), 2.01(3H), 2.40(2H), 3.17(2H), 3.65(2H), 3.97(6H), 4.96(1H)

TABLE 2-continued

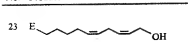
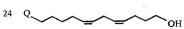
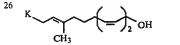
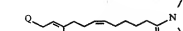
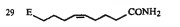
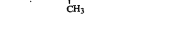
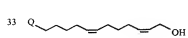
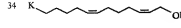
Ex. No.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
23		7*	$C_{19}H_{26}O_3$ (302.42)	1.3–1.6(4H), 1.8–2.2 (3H), 2.03(9H), 2.07 (3H), 2.50(2H), 2.84 (2H), 4.26(2H), 5.3–5.8(4H)
24		4*	$C_{21}H_{30}O_5$ (362.47)	1.3–1.8(7H), 1.9–2.3 (4H), 2.00(3H), 2.46 (2H), 2.78(2H), 3.64 (2H), 3.97(6H), 5.3–5.5(4H)
25		26	$C_{22}H_{30}O_5$ (374.46)	1.3–1.8(4H), 1.9–2.3 (4H), 2.00(3H), 2.5–2.85(4H), 3.97(6H), 4.26(2H), 5.3–5.8 (6H)
26		18	$C_{24}H_{28}O_3$ (364.46)	1.78(3H), 2.18(3H), 2.4–2.6(4H), 2.85(2H), 3.35(2H), 4.25(2H), 5.0(1H), 5.3–5.8(4H), 7.5–8.2(4H)
27		21*	$C_{36}H_{50}N_2O_8$ (638.81)	1.2–1.8(4H), 1.72(3H), 1.9–2.5(12H), 2.00 (3H), 3.16(2H), 3.4–3.7(6H), 3.42(2H), 3.84(9H), 3.97(6H), 4.93(1H), 5.2–5.4(2H), 6.53(2H)
28		12*	$C_{25}H_{38}NO_3$ (395.55)	1.13(3H), 1.24(3H), 1.4–2.0(6H), 2.0–2.4 (6H), 2.05(6H), 2.08 (3H), 2.53(2H), 3.14 (2H), 4.0–4.4(1H), 5.5–5.7(1H)
29		11*	$C_{18}H_{25}NO_3$ (303.39)	1.3–1.7(6H), 1.9–2.2 (4H), 1.99(9H), 2.47 (2H), 5.3–5.5(2H)
30		11	$C_{20}H_{28}O_5$ (348.45)	1.4–1.9(3H), 1.77(3H), 1.9–2.6(6H), 2.16(3H), 3.3?(2H), 3.7(2H), 3.93(6H), 5.18(1H), 5.74(1H), 5.79(1H)
31		46	$C_{21}H_{26}O_5$ (358.44)	1.4–1.8(7H), 2.1–2.4 (6H), 2.03(3H), 2.47 (2H), 3.97(6H), 4.22 (2H)
32		47	$C_{23}H_{24}O_3$ (348.45)	1.5–1.8(6H), 1.81(1H), 2.1–2.4(6H), 2.20(3H), 2.64(2H), 4.20(2H), 7.6–7.8(2H), 8.0–8.2 (2H), m.p. 97–98° C.
33		48	$C_{21}H_{30}O_5$ (362.47)	1.2–1.7(7H), 1.9–2.3 (6H), 2.00(3H), 2.44 (2H), 3.97(6H), 4.0–4.2(2H), 5.3–5.6(4H)
34		49	$C_{23}H_{28}O_3$ (352.48)	1.2–1.7(7H), 1.9–2.3 (6H), 2.18(3H), 2.63 (2H), 4.0–4.2(2H), 5.3–5.6(4H), 7.6–7.8 (2H), 8.0–8.2(2H)

TABLE 2-continued

Ex. No.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
35		30	$C_{21}H_{38}O_3$ (330.47)	1.2–1.6(7H), 1.8–2.2 (6H), 2.01(9H), 2.48 (2H), 4.0–4.2(2H), 5.3–5.6(4H)

Note:
The Number marked by * means Example No.

The following reference examples illustrate the production of the starting compounds utilized in the above examples.

REFERENCE EXAMPLE 1

A solution of tetrahydropyranyl ether of propargyl alcohol (16.8 g, 0.12 mmole) in ether (15 ml) was added dropwise to the freshly prepared sodium amide (2.88 g of sodium and 50 mg of ferric nitrate) in liquid ammonia (300 ml) under argon atmosphere at −60° C. to −40° C. over a 20-minute period, and the mixed solution was stirred under the same conditions for 40 minutes. A solution of the compound produced in Reference Example 29 (IV, R^1=R^2=OCH_3, R^3=CH_3, m=0, n=4, Z=I, 39.4 g, 0.10 mole) in ether (40 ml) was added dropwise to the reaction solution at −60° to −50° C. over a 40-minute period, followed by stirring under the same conditions for 1 hour. Ammonium chloride (50 g) was added to the reaction solution, and ammonia was removed under reduced pressure. Then, isopropyl ether (300 ml) and water (300 ml) were added, and the product was extracted. The organic layer was washed with two portions of saturated aqueous ammonia (300 ml) and dried (over $MgSO_4$), and the solvent was distilled off, leaving a residue. The residue was dissolved in methanol (300 ml), and p-toluenesulfonic acid (0.95 g) was added, followed by stirring at 70° C. for 0.5 hour. After the solution was cooled, aqueous sodium bicarbonate solution (50 ml) was added, and the methanol was distilled off under reduced pressure. To the residue were added isopropyl ether (300 ml) and water (200 ml) for extraction. The organic layer was washed with an aqueous sodium chloride solution and dried (over $MgSO_4$), and the solvent was distilled off under reduced pressure. The residue was chromatographed on a column of silica gel developing with isopropyl ether-ethyl acetate (49:1) to give 1,2,3,4-tetramethoxy-5-methyl-6-(7-hydroxy-5-heptynyl)benzene (II,R^1=R^2=OCH_3, R^3=CH_3, m=0, n=4, X=—C≡C—, n'=1, k=1, Y^2=OH, 27.4 g, 85%). As to the physical properties, see Table 3 (the same shall apply hereinafter).

REFERENCE EXAMPLES 2 TO 10

By the procedure of Reference Example 1, there were obtained the compounds as shown in Table 3.

REFERENCE EXAMPLE 11

In the same manner as in Reference Example 1, 2,3-dimethoxy-1,4-bismethoxymethyloxy-5-methyl-6-(6-iodo-3-methyl-2-hexenyl)-benzene (IV, R^1=OCH_3, R^2=OCH_2OCH_3, R^3=CH_2OCH_3, m=1, n=2, Z=I, 2.37 g, 4.8 mmole) produced in Reference Example 28 was allowed to undergo the coupling reaction with 2-tetrahydropyranyl ether of 3-butyn-1-ol (0.96 g, 5.3 mmole) in the presence of sodium amide (0.14 g as sodium) in liquid ammonia (30 ml). After the completion of the reaction, ammonium chloride (5 g) was added, and the ammonia was removed under reduced pressure. Water was added to the residue, and the product was extracted with isopropyl ether (100 ml). The organic layer was washed with water, dried and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel developing with isopropyl ether to give 2,3-dimethoxy-1,4-bismethoxymethyloxy-5-methyl-6-[10-(2-tetrahydropyranyloxy)-3-methyl-7-yn-2-decenyl]benzene (II, R^1=OCH_3, R^2=OCH_2OCH_3, R^3=—CH_2OCH_3, m=1, n=2, k=1, X=—C≡C—, n'=2,

2.07 g, 83%).

REFERENCE EXAMPLE 12

Anhydrous dimethyl sulfoxide (12 ml) was added to sodium hydride (1.44 g, 60 mmole) in an atmosphere of argon, and the mixture was stirred at 65° to 70° C. for 1 hour. After cooling at 10° to 15° C., a solution of 5-carboxypentyltriphenylphosphonium bromide (VIII, n'=5, Y^2=COOH, 13.7 g, 30 mmole) in anhydrous dimethyl sulfoxide (70 ml) was added dropwise to the mixture over a 30-minute period, followed by stirring under cooling with water for 15 minutes. A solution of 2,3,5-trimethyl-1,4-dimethoxy-6-(3-formylpropyl)-benzene (V, R^1=R^3=CH_3, R^2=OCH_3, m=0, n=4, 5.0 g, 20 mmole) produced in Reference Example 44 in dimethyl sulfoxide (20 ml) was added dropwise to the mixture over a 20-minute period, followed by stirring at room temperature for 40 minutes. After the completion of the reaction, 10% aqueous phosphoric acid solution (40 ml), isopropyl ether (250 ml) and water (150 ml) were added successively, and the product was extracted. The organic layer was washed with aqueous sodium chloride solution, dried (over $MgSO_4$) and concentrated. Then, the residue was chromatographed on a column of silica gel developing with isopropyl ether-ethyl acetate (98:2) to give 2,3,5-trimethyl-1,4-dimethoxy-6-(9-carboxy-(4Z)-nonenyl)-benzene (II, R^1=R^3=CH_3, R^2=OCH_3, m=0, k=1, n=4, X=$\overset{H}{>}\times\overset{H}{<}$, n'=5, Y^2=COOH, 5.66 g, 81%).

REFERENCE EXAMPLES 13 TO 15

By the procedure of Reference Example 12, there were produced the compounds as shown in Table 3.

REFERENCE EXAMPLE 16

In ethyl acetate (10 ml) was dissolved 1,2,3,4-tetramethoxy-5-methyl-6-(12-hydroxy-5,8-dodecadiynyl)-benzene (II, 500 mg, 1.2 mmole) produced in Reference Example 24, and, after the addition to the solution of the Lindlar catalyst (48 mg) and quinoline (7 μl), hydrogenation was carried out at room temperature. At the time when the theoretical amount of hydrogen was absorbed, the reaction was suspended, and the catalyst was removed, followed by distilling off the solvent under reduced pressure. The residue was chromatographed on a column of silica gel, developing with isopropyl ether to give 1,2,3,4-tetramethoxy-5-methyl-6-(12-hydroxy-(5Z,8Z)-dodecadienyl)-benzene (II, 470 mg, 93%)

REFERENCE EXAMPLES 17 TO 18

By the procedure of Reference Example 16, there were produced the compounds as shown in Table 3.

REFERENCE EXAMPLE 19

A tetrahydrofuran solution of 2,3,5-trimethyl-1,4-dimethoxy-6-(7-iodohept-5-ynyl)-benzene (II-1a, $R^1=R^3=CH_3$, $R^2=OCH_3$, m=0, n=4, X=—C≡C—, k=1, n'=1, Z=I, 4.00 g, 10 mmole) obtained in Reference Example 33 was added dropwise over a 20-minute period to a solution of Grignard reagent in tetrahydropyran ether of propargyl alcohol prepared in advance in an atmosphere of argon [which was prepared by reaction of ethylmagnesium bromide in tetrahydrofuran (50 ml) under argon, prepared from magnesium (0.27 g) and ethyl bromide (1.31 g), adding a solution of tetrahydropyranyl ether of propargyl alcohol (1.56 g) in tetrahydrofuran (5 ml) over a 20-minute period, stirring the mixture at 50° C. for 1 hour, cooling the reaction solution to room temperature, adding cuprous bromide (30 mg) and stirring at room temperature for 15 minutes], and the mixture was stirred at 50° C. for 2 hours. The reaction solution was cooled, after the completion of the reaction, and aqueous ammonium chloride solution (30 ml) was added, followed by stirring. The tetrahydrofuran was distilled off under reduced pressure, and the product was extracted with isopropyl ether (50 ml). The organic layer was washed with aqueous ammonium chloride solution (30 ml) and dried (over $MgSO_4$), and the solvent was distilled off. The residue was dissolved in methanol (50 ml), and p-toluenesulfonic acid (0.1 g) was added, followed by heating at 70° C. Following the cooling, aqueous sodium bicarbonate solution (20 ml) was added, and the methanol was distilled off under reduced pressure. Isopropyl ether (100 ml) and water (50 ml) were added to the residue, and the product was extracted. The organic layer was washed with aqueous sodium chloride solution and dried (over $MgSO_4$), and the solvent was distilled off under reduced pressure. The residue was chromatographed on a column of silica gel developing with isopropyl ether to give 2,3,5-trimethyl-1,4-dimethoxy-6-(10-hydroxydeca-5,8-diynyl)-benzene (II, $R^1=R^3=CH_3$, $R^2=OCH_3$, m=0, n=4, X=—C≡C—, n'=1, k=2, Y^2=OH, 2.44 g, 74%).

REFERENCE EXAMPLES 20 TO 27

By the procedure of Reference Example 19, there were obtained the compounds as shown in Table 3.

REFERENCE EXAMPLE 28

In methylene chloride (250 ml) were dissolved 2,3,5-trimethyl-1,4-dimethoxy-6-(4-hydroxybutyl)-benzene (VI, $R^1=R^3=CH_3$, $R^2=OCH_3$, m=0, n=4, 26.1 g, 0.104 mole) and triethylamine (21.8 ml, 0.104×1.5 mole), and the solution was stirred under cooling with ice. A solution of methanesulfonyl chloride (14.3 g, 0.104×1.2 mole) in methylene chloride (30 ml) was added dropwise to the solution over a 30-minute period, followed by stirring under cooling with ice for 30 minutes. After the completion of the reaction, the organic layer was washed with ice water (250 ml), 10% aqueous, cold hydrochloric acid (250 ml), aqueous saturated sodium bicarbonate solution (250 ml) and aqueous sodium chloride solution (250 ml), successively, dried (over $MgSO_4$) and concentrated. The residual solution was dissolved in acetone (300 ml), to which sodium iodide (39.0 g) was added, and the reaction was allowed to proceed at 50° C. for 2 hours. After the completion of the reaction, the acetone was distilled off under reduced pressure, and to the residue were added isopropyl ether (300 ml) and H_2O (200 ml) for extraction of the product. The organic layer was washed with 5% aqueous sodium hydrosulfite solution (200 ml) and aqueous sodium chloride solution (200 ml), successively, and dried (over $MgSO_4$), followed by distilling off the solvent. The residue was chromatographed on a column of silica gel developing with a mixed solvent of hexane:isopropyl ether (3:1 to 2:1) to give 2,3,5-trimethyl-1,4-dimethoxy-6-(4-iodobutyl)benzene (IV, $R^1=R^3=CH_3$, $R^2=OCH_3$, m=0, n=4, Z=I, 35.3 g, 94%).

REFERENCE EXAMPLES 29 TO 41

By the procedure of Reference Example 28, there were obtained the products as shown in Table 3.

REFERENCE EXAMPLE 42

In anhydrous dimethyl sulfoxide (75 ml) were dissolved 1,2,3,4-tetramethoxy-5-methyl-6-(4-hydroxybutyl)benzene (VI, $R^1=R^2=OCH_3$, $R^3=CH_3$, m=0, n=4, 14.2 g, 50 mmole) and triethylamine (56.0 ml), and the solution was stirred at room temperature. A solution of sulfur trioxide pyridine complex (31.8 g, 200 mmole) in anhydrous dimethyl sulfoxide (75 ml) was added dropwise to the solution over a 25-minute period, followed by stirring at room temperature for 35 minutes. The reaction solution was poured into ice-water (300 g), and the product was extracted with isopropyl ether (500 ml). The isopropyl ether layer was washed with 10% aqueous phosphoric acid solution and aqueous sodium chloride solution, successively, and dried (over $MgSO_4$), and the solvent was distilled off. The residue was distilled under reduced pressure, thereby yielding 1,2,3,4-tetramethoxy-5-methyl-6-(3-formylpropyl)-benzene (V, $R^1=R^2=OCH_3$, $R^3=CH_3$, m=0, n=4, 11.3 g, 80%, $bp_{0.7}$ 137° to 140° C.).

REFERENCE EXAMPLES 43 TO 44

By the procedure of Reference Example 42, there were obtained the compounds as shown in Table 3.

REFERENCE EXAMPLE 45

In dimethyl sulfoxide (4 ml) was dissolved 2,3,5-trimethyl-1,4-dimethoxy-6-(12-iodo-5,8-dodecadiynyl)-benzene (0.47 g, 1.0 mmole) produced in Reference Example 35, and sodium cyanide (98 mg, 2.0 mmole) was added, followed by stirring at room temperature

for 1 hour. Ether (20 ml) and water (10 ml) were added for extraction of the product. The organic layer was washed with aqueous sodium chloride solution and dried (over $MgSO_4$), and the solvent was distilled off. The residue was chromatographed on a column of silica gel developing with isopropyl ether to give 2,3,5-trimethyl-1,4-dimethoxy-6-(12-cyano-5,8-dodecadiynyl)-benzene (II, 0.24 g, 66%).

REFERENCE EXAMPLE 46

Sodium amide (1.01 g, 20.0×1.3 mmole) was suspended in anhydrous tetrahydrofuran (10 ml), and the suspension was stirred under a stream of nitrogen at room temperature, followed by adding dropwise a solution of 1-(2-tetrahydropyranyloxy)-2,7-octadiyne (4.12 g, 20.0 mmole) in anhydrous tetrahydrofuran over a 30-minute period. Following the dropwise addition, the reaction temperature was increased to 50° C., and the reaction was conducted under stirring for 1.5 hours. The reaction mixture was cooled with ice and, after the addition of hexamethylphosphoramide (5 ml), a solution of 5-methyl-1,2,3,4-tetramethoxy-6-[1-(4-iodobutyl)]-benzene (7.88 g, 20.0 mmole) in anhydrous tetrahydrofuran (20 ml) was added dropwise over a 30-minute period, followed by stirring under the same conditions for 30 minutes and then at room temperature for 1 hour. To the reaction mixture were added ammonium chloride (1.4 g) and water (20 ml) for decomposition of excess reagents. Tetrahydrofuran was distilled off under reduced pressure, and to the residue were added isopropyl ether (100 ml) and water (50 ml) for extraction of the product. The organic layer was washed with aqueous sodium chloride solution and dried (over $MgSO_4$), and the solvent was removed under reduced pressure. The residue was dissolved in methanol (40 ml), and p-toluenesulfonic acid (0.19 g) was added, followed by stirring at 70° C. for 30 minutes. After the cooling, sodium bicarbonate (1 g) was added, and the mixture was concentrated under reduced pressure. To the residue were added isopropyl ether (100 ml) and water (50 ml) for extraction of the product. The organic layer was washed with aqueous sodium chloride solution, dried (over $MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on a column of silica gel developing with an isopropyl ether hexane mixed solvent to give 5-methyl-1,2,3,4-tetramethoxy-6-(12-hydroxy-5,10-dodecadiynyl)benzene (5.33 g, 75%, oil).

REFERENCE EXAMPLE 47

By condensing 1,4-dimethoxy-2-methyl-3-(4-iodobutyl)naphthalene (3.84 g, 10 mmole) with 1-(2-tetrahydropyranyloxy)-2,7-octadiyne (2.10 g, 10 mmole) in accordance with the procedure of the above Reference Example 46, there was produced 1,4-dimethoxy-2-methyl-3-(12-hydroxy-5,10-dodecadiynyl)naphthalene (2.78 g, 73.5%, oily product). 1,4-Dimethoxy-2-methyl-3-(4-iodobutyl)naphthalene [δ1.5 to 2.2(4H), 2.40(3H), 2.82(2H), 3.23(2H), 3.84(3H), 3.87 (3H), 7.3 to 7.5(2H), 7.8 to 8.1(2H)] as utilized in this Reference Example was produced from 1,4-dimethoxy-2-methyl-3-(4-hydroxybutyl)naphthalene [oily substance, NMR ($CDCl_3$), δ1.5 to 1.8(5H), 2.39(3H), 2.81(2H), 3.67(2H), 3.84(3H), 3.87(3H), 7.3 to 7.5(2H), 7.9 to 8.1(2H)] in accordance with the procedure described in Japanese Patent Application No. 49433/'80.

REFERENCE EXAMPLES 48 TO 50

By partially reducing with the Lindlar catalyst the compounds containing triple bond produced in the above Reference Examples 6, 46 and 47 in accordance with Reference Example 16, there were produced the corresponding compounds (see Table 3).

TABLE 3

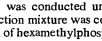
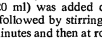
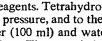
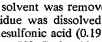
Ref. Ex.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
1		29	$C_{18}H_{36}O_5$ (322.41)	1.4–1.7(4H), 1.81(1H), 2.16(3H), 2.26(2H), 2.57(2H), 3.76(3H), 3.80(3H), 3.87(6H), 4.22(2H)
2		29	$C_{20}H_{30}O_5$ (350.46)	1.4–1.8(7H), 2.1–2.3 (4H), 2.16(3H), 2.56 (2H), 3.71(2H), 3.76 (3H), 3.80(3H), 3.88 (6H)
3		31	$C_{25}H_{36}O_5$ (416.56)	1.4–2.0(9H), 2.1–2.4 (8H), 2.21(3H), 2.63 (3H), 3.71(2H), 3.87 (3H), 3.91(3H), 3.99 (6H)
4		32	$C_{18}H_{26}O_3$ (290.41)	1.5–1.7(4H), 1.77(1H), 2.1–2.3(2H), 2.16(6H), 2.20(3H), 2.60(2H), 3.62(3H), 3.64(3H), 4.19(2H): m.p. 65–66° C.
5		32	$C_{20}H_{30}O_3$ (318.46)	1.5–1.8(7H), 2.1–2.3 (4H), 2.16(6H), 2.20 (3H), 2.60(2H), 3.62 (3H), 3.64(3H), 3.71 (2H)

TABLE 3-continued

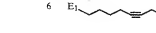
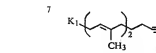
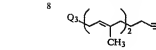
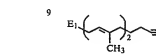
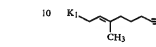
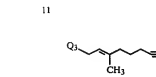
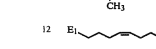
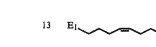
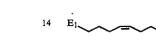
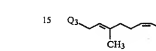
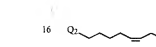
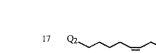
Ref. Ex.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
6		34	$C_{23}H_{32}O_3$ (356.51)	1.4–2.0(7H), 2.1–2.4 (6H), 2.20(6H), 2.25 (3H), 2.64(2H), 3.69 (3H), 3.72(3H), 4.24 (2H)
7		40	$C_{28}H_{36}O_3$ (420.57)	1.56(3H), 1.84(3H), 2.33(3H), 3.82(6H), 4.22(2H), 5.1(2H), 7.2–8.2(4H)
8		37	$C_{28}H_{42}O_7$ (490.62)	1.62(3H), 1.79(3H), 1.9–2.5(6H), 2.20(3H), 3.25(2H), 3.62(3H), 3.64(3H), 3.92(6H), 4.23(2H), 5.13(4H), 5.1(2H)
9		38	$C_{26}H_{38}O_3$ (398.56)	1.61(3H), 1.76(3H), 1.8–2.4(6H), 2.16(3H), 3.20(2H), 3.68(3H), 3.70(3H), 4.23(2H), 5.1(2H)
10		39	$C_{23}H_{28}O_3$ (352.45)	1.86(3H), 2.33(3H), 1.8–2.2(4H), 3.35(2H), 3.48(2H), 3.81(6H), 4.22(2H), 5.1(1H), 7.2–8.2(4H)
11		28	$C_{29}H_{44}O_8$ (520.64)	1.62(3H), 1.79(3H), 2.20(3H), 3.24(2H), 3.4–4.14(H), 3.62(3H), 3.64(3H), 3.92(6H), 4.72(1H), 5.0(1H), 5.13(4H)
12		44	$C_{23}H_{32}O_4$ (348.49)	1.3–1.8(6H), 1.9–2.3 (4H), 2.16(6H), 2.20 (3H), 2.35(2H), 2.62 (2H), 3.62(3H), 3.65 (3H), 5.3–5.5(2H)
13		44	$C_{22}H_{34}O$ (362.51)	1.3–1.8(6H), 1.9–2.2 (4H), 2.16(6H), 2.20 (3H), 2.32(2H), 2.61 (2H), 3.62(3H), 3.65 (6H), 5.3–5.5(2H)
14		44	$C_{21}H_{34}O_3$ (334.50)	1.3–1.7(9H), 1.9–2.2 (4H), 2.16(6H), 2.20 (3H), 2.61(2H), 3.60 (2H), 3.62(3H), 3.64 (3H), 5.3–5.5(2H)
15		43	$C_{26}H_{40}O_8$ (480.61)	1.2–1.8(4H), 1.75(3H), 1.8–2.2(6H), 2.16(3H), 2.33(2H), 3.36(2H), 3.56(3H), 3.58(3H), 3.85(6H), 4.9–5.1(1H), 5.04(4H), 5.2–5.4(2H)
16		24	$C_{23}H_{36}O_5$ (392.54)	1.3–1.9(7H), 1.9–2.3 (4H), 2.19(3H), 2.62 (2H), 2.84(2H), 3.71 (2H), 3.85(3H), 3.89 (3H), 3.98(6H), 5.4–5.6(4H)
17		3	$C_{25}H_{40}O_5$ (420.60)	1.3–1.8(9H), 1.9–2.3 (8H), 2.21(3H), 2.62 (2H), 3.72(2H), 3.85 (3H), 3.89(3H), 3.99 (6H), 5.4–5.6(4H)

TABLE 3-continued

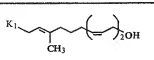
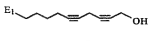
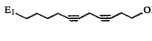
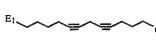
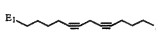
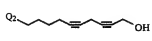
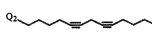
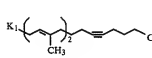
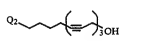
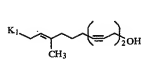
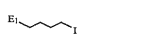
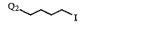
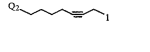
Ref. Ex.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
18		7	$C_{26}H_{34}O_3$ (394.53)	1.86(3H), 2.33(3H), 2.0–2.5(6H), 2.85(2H), 3.50(2H), 3.81(6H), 4.26(2H), 5.0–5.8(5H), 7.2–8.2(4H)
19		33	$C_{21}H_{28}O_3$ (328.46)	1.5–1.7(5H), 2.1–2.3 (2H), 2.16(6H), 2.20 (3H), 2.60(2H), 3.13 (2H), 3.62(3H), 3.64 (3H), 4.20(2H)
20		33	$C_{22}H_{30}O_3$ (342.48)	1.5–1.7(4H), 1.92(1H), 2.1–2.3(2H), 2.16(6H), 2.21(3H), 2.41(2H), 2.60(2H), 3.09(2H), 3.62(3H), 3.64(3H), 3.66(2H)
21		33	$C_{23}H_{32}O_3$ (356.51)	1.5–2.0(7H), 2.1–2.3 (4H), 2.16(6H), 2.20 (3H), 2.60(2H), 3.07 (2H), 3.62(3H), 3.64 (3H), 3.70(2H)
22		33	$C_{24}H_{32}O_4$ (384.52)	1.5–1.9(6H), 2.1–2.3 (4H), 2.15(6H), 2.20 (3H), 2.46(2H), 2.60 (2H), 3.07(2H), 3.62 (3H), 3.64(3H)
23		30	$C_{21}H_{28}O_5$ (360.46)	1.4–1.8(4H), 1.94(1H), 2.1–2.3(2H), 2.16(3H), 2.57(2H), 3.14(2H), 3.76(3H), 3.80(3H), 3.87(6H), 4.22(2H)
24		30	$C_{23}H_{32}O_5$ (388.51)	1.4–1.9(7H), 2.1–2.4 (4H), 2.16(3H), 2.57 (2H), 3.06(2H), 3.70 (2H), 3.76(3H), 3.80 (3H), 3.87(6H)
25		40	$C_{13}H_{40}O_4$ (476.63)	1.55(3H), 1.83(3H), 2.33(3H), 3.50(2H), 3.81(6H), 5.05(2H), 7.2–8.2(4H)
26		36	$C_{26}H_{30}O_5$ (398.48)	1.4–1.8(4H), 1.90(1H), 2.1–2.3(2H), 2.16(3H), 2.58(2H), 3.14(2H), 3.20(2H), 3.76(3H), 3.80(3H), 3.87(6H), 4.23(2H)
27		41	$C_{26}H_{32}O_3$ (392.52)	1.86(3H), 2.33(3H), 1.8–2.4(4H), 2.40(2H), 3.15(2H), 3.50(2H), 3.81(6H), 5.1(1H), 7.2–8.2(4H)
28		—	$C_{15}H_{23}O_2I$ (362.25)	1.4–1.7(2H), 1.91(2H), 2.16(6H), 2.20(3H), 2.61(2H), 3.20(2H), 3.62(3H), 3.64(3H)
29		—	$C_{15}H_{23}O_4I$ (394.25)	1.4–1.7(2H), 1.90(2H), 2.15(3H), 2.59(2H), 3.20(2H), 3.76(3H), 3.80(3H), 3.87(6H)
30		—	$C_{18}H_{25}O_4I$ (432.30)	1.4–1.8(4H), 2.20(3H), 2.2–2.4(2H), 2.61(2H), 3.75(2H), 3.83(3H), 3.88(3H), 3.95(6H)

TABLE 3-continued

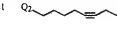
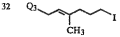
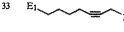
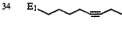
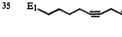
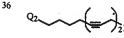
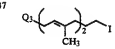
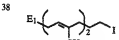
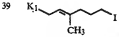
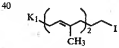
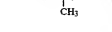
Ref. Ex.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
31		—	$C_{20}H_{29}O_4I$ (460.36)	1.4–1.8(6H), 1.9–2.4 (4H), 2.19(3H), 2.60 (2H), 3.29(2H), 3.81 (3H), 3.85(3H), 3.92 (6H)
32		—	$C_{20}H_{31}O_6I$ (494.37)	1.79(3H), 1.9–2.3(4H), 2.20(3H), 3.26(2H), 3.42(2H), 3.62(3H), 3.64(3H), 3.91(6H), 5.13(4H), 5.18(1H)
33		—	$C_{18}H_{25}O_2I$ (400.30)	1.5–1.7(4H), 2.1–2.3 (2H), 2.16(6H), 2.20 (3H), 2.60(2H), 3.62 (3H), 3.64(3H), 3.66 (2H)
34		—	$C_{20}H_{29}O_2I$ (428.36)	1.4–1.8(6H), 1.9–2.4 (4H), 2.21(6H), 2.26 (3H), 2.65(2H), 3.34 (2H), 3.71(3H), 3.73 (3H)
35		—	$C_{21}H_{31}O_2I$ (466.41)	1.5–1.8(4H), 1.8–2.4 (6H), 2.23(6H), 2.27 (3H), 2.67(2H), 3.16 (2H), 3.34(2H), 3.72 (3H), 3.74(3H)
36		—	$C_{21}H_{27}O_4I$ (470.35)	1.4–1.8(4H), 2.20(3H), 2.0–2.4(2H), 2.62(2H), 3.21(2H), 3.76(2H), 3.81(3H), 3.85(3H), 3.92(6H)
37		—	$C_{25}H_{39}O_6I$ (562.48)	1.62(3H), 1.79(3H), 1.9–2.4(6H), 2.20(3H), 3.26(2H), 3.43(2H), 3.62(3H), 3.64(3H), 3.91(6H), 5.13(4H), 5.1(2H)
38		—	$C_{23}H_{35}O_2I$ (470.43)	1.61(3H), 1.76(3H), 1.8–2.4(6H), 2.16(3H), 3.20(2H), 3.42(2H), 3.68(3H), 3.70(3H), 5.1(2H)
39		—	$C_{20}H_{25}O_2I$ (424.32)	1.86(3H), 2.33(3H), 1.8–2.2(4H), 3.36(2H), 3.50(2H), 3.82(6H), 5.1(1H), 7.2–8.2(4H)
40		—	$C_{25}H_{33}O_2I$ (492.44)	1.56(3H), 1.83(3H), 2.33(3H), 3.34(2H), 3.50(2H), 3.81(6H), 5.1(2H), 7.2–8.2(4H)
41		—	$C_{23}H_{27}O_2I$ (462.37)	1.86(3H), 2.33(3H), 1.8–2.4(4H), 2.44(2H), 3.50(2H), 3.75(2H), 3.81(6H), 7.2–8.2(4H)
42		—	$C_{15}H_{22}O_5$ (282.34)	1.78(2H), 2.16(3H), 2.4–2.7(4H), 3.76(3H), 3.79(3H), 3.88(6H), 9.75(1H), b.p.0.7 135–140° C.
43		—	$C_{20}H_{30}O_7$ (382.46)	1.76(3H), 2.14(3H), 2.2–2.6(4H), 3.36(2H), 3.54(3H), 3.56(3H), 3.84(6H), 5.03(4H), 5.08(1H), 9.71(1H)

TABLE 3-continued

Ref. Ex.	Product	Starting material (Ref. Ex.)	Formula (M.W.)	NMR[in $CDCl_3$, TMS internal standard, δ(ppm)]
44	E_1 CHO	—	$C_{15}H_{22}O_3$ (250.34)	1.80(2H), 2.16(6H), 2.21(3H), 2.4–2.7(4H), 3.62(6H), 9.76(1H), b.p.$_1$ 130–140° C.
45	E_1 CN	—	$C_{24}H_{31}NO_2$ (365.52)	1.4–2.0(6H), 2.1–2.4 (4H), 2.19(6H), 2.24 (3H), 2.4–2.8(4H), 3.13(2H), 3.70(3H), 3.73(3H)
46	Q_2 OH	—	$C_{23}H_{32}O_5$ (388.51)	1.4–1.8(7H), 2.1–2.4 (6H), 2.17(3H), 2.67 (2H), 3.76(3H), 3.80 (3H), 3.88(6H), 4.20 (2H)
47	K_1 OH	—	$C_{25}H_{30}O_3$ (378.52)	1.5–1.8(7H), 2.1–2.4 (6H), 2.41(3H), 2.80 (2H), 3.85(3H), 3.89 (3H), 4.20(2H), 7.3–7.5(2H), 7.9–8.1(2H)
48	Q_2 OH	46	$C_{23}H_{36}O_5$ (392.54)	1.2–1.7(7H), 1.9–2.3 (6H), 2.14(3H), 2.55 (2H), 3.76(3H), 3.79 (3H), 3.87(6H), 4.0–4.2(2H), 5.3–5.6(4H)
49	K_1 OH	47	$C_{25}H_{38}O_3$ (382.55)	1.2–1.7(7H), 1.9–2.3 (6H), 2.39(3H), 2.79 (2H), 3.84(3H), 3.87 (3H), 4.0–4.2(2H), 5.3–5.6(4H), 7.3–7.5 (2H), 7.9–8.1(2H)
50	E_1 OH	6	$C_{23}H_{26}O_3$ (360.54)	1.2–1.6(7H), 1.9–2.2 (6H), 2.16(6H), 2.19 (3H), 2.58(2H), 3.62 (3H), 3.64(3H), 4.0–4.2(2H), 5.3–5.6(4H)

REFERENCE EXAMPLE 51

In toluene (500 ml) was suspended 2,3,5-trimethylphenyl (100 g, 0.735 mole), and to the suspension were added dihydrofuran (56.6 g, 0.735×1.1 mole) and camphorsulfonic acid (0.85 g), followed by stirring at room temperature for 30 minutes. As the reaction proceeded, there occurred dissolution under the evoluation of heat. Without isolating and purifying tetrahydrofur-2-yl ether as produced, camphorsulfonic acid (16.1 g) was further added to the reaction solution, followed by stirring at 60° C. for 1.5 hours. After the conclusion of the reaction, the reaction solution was cooled, and saturated sodium hydrogen carbonate (300 ml) was added for neutralization. The organic layer was washed with water, dried (over $MgSO_4$) and freed of the solvent by distillation. The residue was distilled under reduced pressure, thereby yielding 2,3,5-trimethyl-6-(tetrahydrofur-2-yl)phenyl (147 g, 97%, bp$_{1.0}$ 124° to 130° C.).

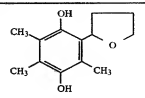
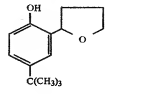
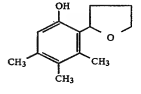
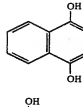
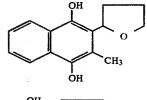
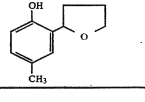
REFERENCE EXAMPLE 52

In toluene (150 ml) was suspended 2,3-dimethoxy-5-methyl-1,4-benzohydroquinone (18.2 g, 0.1 mole), and to the suspension were added dihydrofuran (15 g, 0.204 mole) and camphorsulfonic acid (0.15 g), followed by stirring at room temperature for 1 hour. Without isolating the product, camphorsulfonic acid (2.2 g) was further added to the reaction solution, followed by stirring at 60° C. for 3 hours. The reaction solution was cooled, washed with water, dried (over $MgSO_4$) and freed of the solvent by distillation. The residue was chromatographed on a column of silica gel, and developing with isopropyl ether yielded 2,3-dimethoxy-5-methyl-6-(tetrahydrofur-2-yl)-1, 4-benzyhydroquinone (20.8 g, 82%, mp. 77° to 78° C.).

REFERENCE EXAMPLES 53 TO 57

By the same procedures as described in Reference Example 51 (Method A) and 52 (Method B), where were obtained the compounds as shown in Table 4.

TABLE 4

Ref. Ex.	Starting material	Method	Product	Yield	Physical property
53		B		75%	mp. 104–105° C.
54		A		57%	oil IR(cm^{-1}): 3500, 1120
55		A		72%	bp$_{1.0}$ 130–135° C.
56		B		60%	as the quinone form mp. 46–47° C.
57		A		56%	bp$_{0.6}$ 100–106° C.

REFERENCE EXAMPLE 58

In dimethylformamide (200 ml) was dissolved 2,3,5-trimethyl-6-(tetrahydrofur-2-yl)-1,4-benzohydroquinone (22.2 g, 0.1 mole). The solution was cooled with ice under a nitrogen atmosphere, and 60% sodium hydride (oilborne, 8.8 g, 0.10×2.2 mole) was added, followed by stirring for 15 minutes. Then, methyl iodide (35.5 g, 0.10×2.5 mole) was added dropwise to the mixture over a 15-minute period, followed by stirring for 30 minutes. Ice-cooled water (250 g) was added to the reaction solution, and the product was extracted with isopropyl ether (500 ml). The extract was washed with water, dried and freed of the solvent. The residue was distilled under reduced pressure, thereby yielding 1,4-dimethoxy-2,3,5-trimethyl-6-(tetrahydrofur-2-yl)benzene (24.5 g, 98%, bp$_{1.0}$ 130° to 140° C.).

The dimethoxy compound (24.5 g) obtained in this manner was dissolved in ethyl acetate (250 ml) and, following the addition to the solution of 5% palladium-carbon (2.5 g) and 70% perchloric acid (1 ml), catalytic reduction was conducted at 40° C. After the completion of the reaction, the catalyst was filtered out, and the ethyl acetate solution was washed with aqueous saturated sodium hydrogen carbonate and water, successively. The organic layer was separated, dried and freed of the organic solvent under reduced pressure. Recrystallization of the residue from isopropyl ether-hexane yielded 1,4-dimethoxy-2,3,5-trimethyl-6-(4-hydroxybutyl)benzene (22.2 g, 90%, mp. 88° to 88.5° C.).

REFERENCE EXAMPLE 59

By the same procedure as described in Reference Example 58, 2,3-dimethoxy-5-methyl-6-(tetrahydrofur-2-yl)-1,4-benzohydroquinone (27 g, 0.106 mole) was methylated with methyl iodide, thereby being derived into 1,2,3,4-tetramethoxy-5-methyl-6-(tetrahydrofur-2-yl)benzene (28.5 g, 98%, bp$_{1.0}$ 135° to 138° C.). The catalytic reduction of the compound afforded 1,2,3,4-tetramethoxy-5-methyl-6-(4-hydroxybutyl)benzene (28.2 g, 99%, oily substance).

REFERENCE EXAMPLE 60

In anhydrous methylene chloride (300 ml) were 1,2,3,4-tetramethoxy-5-methyl-6-(4-hydroxybutyl)benzene (28.2 g, 0.1 mole) as obtained in Reference Example 59 and triethylamine (16 g, 0.15 mole), and the solution was cooled to 0° C. A solution of methanesulfonyl chloride (14.3 g, 0.12 mole) in methylene chloride (30 ml) was added dropwise to the solution, followed by stirring for 30 minutes. The reaction solution was washed with water, dilute aqueous phosphoric acid and

water, successively, and the organic layer was dried (over $MgSO_4$) and freed of the solvent. Acetone (300 ml) and sodium iodide (39.0 g, 0.26 mole) were added to the residue, and the mixture was warmed at 50° C. for 2 hours. After the completion of the reaction, acetone was distilled off under reduced pressure, and isopropyl ether (300 ml) and water (200 ml) were added to the residue for extraction of the product. The organic layer was washed with 5% aqueous sodium hydrosulfite and water, successively, and dried (over $MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on a column of silica gel, and developing with isopropyl ether-hexane (1:1) yielded 1,2,3,4-tetramethoxy-5-methyl-6-(4-iodobutyl)-benzene (37.0 g, 94%).

REFERENCE EXAMPLE 61

By adding sodium (2.88 g, 0.12 gram atom) and ferric nitrate (50 mg) to liquid ammonia (300 ml), sodium amide was prepared at −60° to −40° C. A solution of 1-tetrahydropyranyloxy-5-hexyne (21.8 g, 0.12 mole) in ether (20 ml) was added to the ammonia solution over a period of 20 minutes, followed by stirring for 40 minutes. A solution of the iodo compound (37.0 g, 0.094 mole) obtained in Reference Example 60 in ether (40 ml) was added dropwise to the mixture over a period of 40 minutes, while maintaining the reaction temperature a −60° to −50° C., followed by stirring at the same temperature for 1 hour and then at −50° to −30° C. for 1 hour. Then, ammonium chloride (50 g) was added to the reaction solution, followed by stirring for 10 minutes. The ammonia was removed, and isopropyl ether (300 ml) and water (300 ml) were added for the extraction of the product. The organic layer was washed with water, dried (over $MgSO_4$) and freed of the solvent by distillation, thereby yielding the crude product. This was dissolved in methanol (300 ml), and p-toluenesulfonic acid (0.95 g) was added to the solution, followed by stirring at 70° C. for 30 minutes. After the solution was cooled, sodium hydrogen carbonate (2 g) was added, and the methanol was distilled off under reduced pressure. The residue was treated with isopropyl ether (300 ml) and water (200 ml) for the extraction of the product. The organic layer was washed with water, dried (over $MgSO_4$) and freed of the solvent by distillation under reduced pressure. The residue was chromatographed on silica gel, and developing with isopropyl ether yielded 1,2,3,4-tetramethoxy-5-methyl-6-(10-hydroxydec-5-ynyl)benzene (29.4 g, 86%).

REFERENCE EXAMPLE 62

In ethanol (200 ml) was dissolved the compound (18.2 g, 0.05 mole) obtained in Reference Example 61, and after 5% palladium-carbon (1 g) was added, the catalytic reduction was carried out. At the time when absorption of hydrogen stopped completely, the reaction was completed. The catalyst was filtered out and the ethanol was removed under reduced pressure. The reduced form (18.2 g, 0.05 mole) and 2,6-dicarboxypyridine-1-oxide (27.4 g) were dissolved in acetonitrile (240 ml) and water (120 ml), and after the solution was cooled with ice, a solution of ceric ammonium nitrate (82.2 g, 0.15 mole) in 50% aqueous acetonitrile (360 ml) was added dropwise over a 1-hour period, followed by stirring under ice-cooling for 30 minutes and at room temperature for 30 minutes. After the conclusion of the reaction, insolubles were filtered out, and the acetonitrile was removed under reduced pressure. The product was extracted with isopropyl ether (500 ml), and the extract was washed with saturated aqueous sodium hydrogen carbonate and water, successively, dried (over $MgSO_4$) and freed of the isopropyl ether. The residue was chromatographed on silica gel, and developing with isopropyl ether yielded 2,3-dimethoxy-5-methyl-6-(10-hydroxydec-5-ynyl)-1,4-benzoquinone (14.5 g, 86%, mp. 52° to 53° C.).

REFERENCE EXAMPLE 63

By subjecting 1,4-dimethoxy-2,3,5-trimethyl-6-(4-hydroxybutyl)benzene obtained in Reference Example 58 to the same reaction as described in Reference Example 60 to 62, there was obtained 2,3,5-trimethyl-6-(10-hydroxydec-5-ynyl)-1,4-benzoquinone (65° to 66° C.).

REFERENCE EXAMPLE 64

In ethyl acetate (50 ml) was dissolved 2,3,5-trimethyl-6-(tetrahydrofur-2-yl)-1,4-benzohydroquinone (2.24 g, 0.01 mole) obtained in Reference Example 53, and after perchloric acid (0.1 ml) and 5% palladium-carbon (500 mg) were added to the solution, the catalytic reduction was carried out at 100 atmospheric pressure. After the completion of the reaction, the catalyst was filtered out, and 5% aqueous solution of ferric chloride (50 ml) was added to the reaction solution, followed by stirring at room temperature for 1 hour. The organic layer was separated, and the water layer was extracted once with ethyl acetate. The extract was combined with the organic layer, followed by washing with water, drying (over $MgSO_4$) and concentrating. The resulting crude product was chromatographed on silica gel, and developing with isopropyl ether-ethyl acetate (95:5) yielded the desired 2,3,5-trimethyl-6-(4-hydroxybutyl)-1,4-benzoquinone (1.9 g, 88%, mp. 36° to 38° C.).

REFERENCE EXAMPLE 65

By subjecting 2,3-dimethoxy-5-methyl-6-(tetrahydrofur-2-yl)-1,4-benzohydroquinone (2.56 g, 0.01 mole) obtained in Reference Example 52 to the same catalytic reduction and oxidation reaction as described in Reference Example 64, there was obtained the desired 2,3-dimethoxy-5-methyl-6-(4-hydroxybutyl)-1,4-benzoquinone (2.17 g, 84%, oily substance).

IR absorptoin spectrum $\nu_{max}^{film}(cm^{-1})$: 3400(OH), 1660, 1640, 1610(quinone).

EXAMPLES OF PHARMACEUTICAL COMPOSITION

(A) Capsule	
(1) Compound of Example 17	50 mg
(2) Cellulose fine powder	30 mg
(3) Lactose	37 mg
(4) Magnesium stearate	3 mg
Total	120 mg

All the materials were mixed and filled into a gelatin capsule.

(B) Soft Capsule	
(1) Compound of Example 31	50 mg
(2) Corn starch oil	100 mg
Total	150 mg

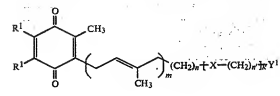
A mixed solution of (1) and (2) were prepared and filled into a soft capsule by a conventional manner.

(C) Tablet	
(1) Compound of Example 32	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (gelatinized)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Calcium carboxymethyl cellulose	20 mg
Total	120 mg

All the materials were mixed and compressed by a tabletting machine to prepare a tablet in accordance with a conventional manner.

What is claimed is:

1. A compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,
Y^1 is hydroxyl,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim **1**, which is 2,3-dimethoxy-5-methyl-6-(9-hydroxynon-5-ynyl)-1,4-benzoquinone.

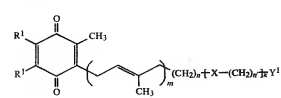
3. The compound according to claim **1**, which is 2,3,5-trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone.

4. The compound according to claim **1**, which is 2,3-dimethoxy-5-methyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone.

5. The compound according to claim **1**, which is 2,3-dimethoxy-5-methyl-6-[12-hydroxy-(Z,Z)-5,10-dodecadienyl]-1,4-benzoquinone.

6. The compound according to claim **1**, which is 2,3,5-trimethyl-6-[12-hydroxy-(Z,Z)-5,10-dodecadienyl]-1,4-benzoquinone.

7. A compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,
Y^1 is hydrogen, carboxyl, cyano, C_{2-4} alkanoyloxy, benzoyloxy or —COZ in which Z is amino or mono- or $di\text{-}C_{1-4}$ alkylamino,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
with the proviso that there are 8–15 carbon atoms in series between the quinone ring and Y^1,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof.

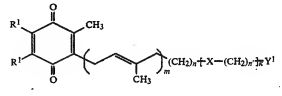
8. A compound according to claim **7**, which is in the quinone form.

9. A compound according to claim **7**, wherein R^1 is methyl or methoxy, X is —C≡C—, and m is zero.

10. A compound according to claim **7**, wherein Y^1 is carboxyl, cyano or —COZ in which Z is amino or C_{1-4} alkylamino.

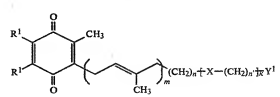
11. A compound according to claim **7**, wherein m is zero or 1, n is an integer of 1 to 4, n' is an integer of 1 to 3 and k is 1 or 2.

12. A pharmaceutical composition suitable for suppressing the production of SRS-A in a mammal which comprises, as an active ingredient, an effective amount of a compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,
Y^1 is hydroxyl,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof,
and a pharmaceutically acceptable carrier or excipient therefor.

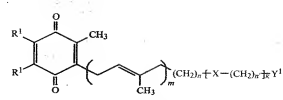
13. A pharmaceutical composition suitable for suppressing the production of SRS-A in a mammal which comprises, as an active ingredient, an effective amount of a compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,

Y^1 is hydrogen, carboxyl, cyano, C_{2-4} alkanoyloxy, benzoyloxy or —COZ in which Z is amino or mono- or di-C_{1-4} alkylamino,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
with the proviso that there are 8–15 carbon atoms in series between the quinone ring and Y^1,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof,
and a pharmaceutically acceptable carrier or excipient therefor.

14. A method for suppressing the production of SRS-A in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,
Y^1 is hydrogen, hydroxyl, carboxyl, cyano, C_{2-4} alkanoyloxy, benzoyloxy or —COZ in which Z is amino or mono- or di-C_{1-4} alkylamino,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof.

* * * * *

REEXAMINATION CERTIFICATE (1090th)

United States Patent [19]

[11] B1 4,393,075

Terao et al.

[45] Certificate Issued Jul. 4, 1989

[54] QUINONE COMPOUNDS AND THEIR USE IN SUPPRESSING THE PRODUCTION OF SRS-A IN MAMMALS

[75] Inventors: Shinji Terao, Toyonaka; Mitsuru Shiraishi, Suita; Yoshitaka Maki, Kyoto, all of Japan

[73] Assignee: Takeda Chemical Industries, Ltd.

Reexamination Request:
No. 90/001,640, Nov. 18, 1988

Reexamination Certificate for:

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Appl. No.:	248,042
Filed:	Mar. 26, 1981

[30] Foreign Application Priority Data

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Apr. 30, 1980 [JP]	Japan	55-58464
Dec. 27, 1980 [JP]	Japan	55-186622

[51] Int. Cl.[4] A61K 31/12; A61K 31/275; C07C 50/00

[52] U.S. Cl. ..... 514/519; 260/396 R; 514/520; 514/532; 514/546; 514/557; 514/559; 514/568; 514/569; 514/621; 514/622; 514/675; 514/678; 514/679; 514/682; 514/826; 558/410; 560/106; 560/107; 560/231; 560/255; 562/466; 562/308; 564/123; 564/180; 568/811; 568/823

[58] Field of Search ..... 260/396 R; 514/520, 514/690, 679, 682, 519

[56] References Cited

U.S. PATENT DOCUMENTS

3,974,187 8/1976 Wan et al. ..... 260/396 R

FOREIGN PATENT DOCUMENTS

52-87130	7/1977	Japan .
896719	5/1962	United Kingdom .
1147612	4/1969	United Kingdom .
1449043	9/1976	United Kingdom .
1512541	6/1978	United Kingdom .

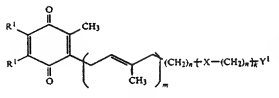
OTHER PUBLICATIONS

Wantanabe et al., Chem. Pharm. Bull., 26(3) 774–783 (1978).

Primary Examiner—Leonard Schenkman

[57] **ABSTRACT**

New quinone compounds of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—; X is —CH=CH— or —C≡C—; Y^1 is hydrogen, hydroxyl, carboxyl, cyano, acyloxy or —COZ in which Z is amino which may be substituted; m is zero or an integer of 1 to 3; n is zero or an integer of 1 to 10; n' is an integer of 1 to 5; k is an integer of 1 to 3; and when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the $—X—(CH_2)_{n'}$ group; and their hydroquinone forms and salts, have useful physiological activities such as antiasthmatic, antiallergic and blood-pressure decreasing activities.

REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets **[ ]** appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

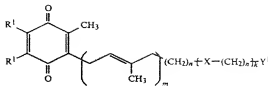
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1–6 and 12–14** is confirmed.

Claim 7 is determined to be patentable as amended.

Claims 8–11, dependent on an amended claim, are determined to be patentable.

7. A compound of the formula:



wherein R^1 is methyl or methoxy, or the two R^1 groups jointly represent —CH=CH—CH=CH—,
X is —CH=CH— or —C≡C—,
Y^1 is **[hydrogen,]** carboxyl, cyano, C_{2-4} alkanoyloxy, benzoyloxy or —COZ in which Z is amino or mono- or di-C_{1-4} alkylamino,
m is zero or an integer of 1 to 3,
n is zero or an integer of 1 to 10,
n' is an integer of 1 to 5,
k is an integer of 1 to 3, and
when k is 2 or 3, n' is optionally variable within the range of 1 to 5 in each occurrence of the —X—$(CH_2)_{n'}$ group,
with the proviso that there are 8–15 carbon atoms in series between the quinone ring and Y^1,
or its hydroquinone form,
or a pharmaceutically acceptable salt thereof.

* * * * *